IMMUNIZATION PRACTICES IN CHILDREN

ASHOK DUTTA

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VIJAY AGARWAL

INDIAN ACADEMY OF PEDIATRICS
DELHI BRANCH
1988

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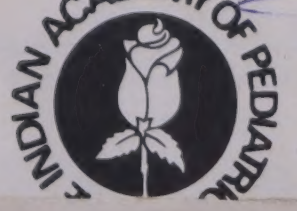
15 Dec '89
New Delhi.



UNITY HEALTH CELL

Immunization Practices in Children

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First Edition 1988
Price Rs. 40
US $ 10.

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Printed and Published by Indian Academy of Pediatrics, Delhi Branch at Anupam Art Printers 6/14, Kirti Nagar Industrial Area, New Delhi-110015. Ph.: 533945 & 505888.

PREFACE

Every nation evolves its own immunization schedule depending on its disease epidemiology, health infrastructure and socio-economic conditions. In India also, a National Schedule has been in vogue ever since EPI was launched in 1978. Subsequently there have been many changes in this schedule like dropping of the second booster of DPT, dropping of typhoid vaccine, advancing the age of first dose of DPT and Polio to 6 weeks and so on. In 1985, Universal Immunization Programme (UIP) was launched, to replace EPI. Under this the emphasis from under fives was shifted to **under ones,** reducing the number of potential beneficiaries from 120 million to just 22 millions annually. It considerably reduced the denominator for calculating the percentage coverage and yet the coverage is far from satisfactory. Greater emphasis on UIP led to its separation from the overall maternal and child health programme with the result that infants would get 5 injections in a year and little else for other aspects of health. This is not to criticise any of these changes or even to doubt their scientific validity but to point out that all these important changes have been brought about without any meaningful discussions with the only professional body of child specialists in this country i.e. the Indian Academy of Pediatrics.

In all advanced countries the professional bodies like ours, play a pivotal role in evolving strategies for immunisation and disease control. Thus the American Academy of Pediatrics has a standing Committee on Infectious disease which brings out periodic recommendations on the proper use of different vaccines which become the reference point for all physicians. But we in the Indian Academy of Pediatrics have so far failed to evolve any such advisory mechanism which could become a rallying point not only to our members but to all the physicians and the government. There have been many workshops on Immunisation particularly in the last year which have focussed attention on implementation, monitoring and evaluation strategies in the UIP — but none of them has directed efforts towards fostering a debate, based on a dispassionate review of literature, regarding various aspects of immunization schedule itself.

A National Workshop was convened in Delhi during September, 1988 with the specific purpose of evolving recommendations on all aspects of immunization practices based entirely on the review of available literature where every aspect of immunization practices in children was examined thread-bare in an entirely scientific manner. The background papers were prepared by comparatively young entrants in the field of pediatrics who were given definite terms of reference and encouraged to review the literature extensively. Each of these papers were then sent to two experts in the respective field for their comments. The papers were presented at the workshop and were discussed among 70 eminent participants from all over the country. The papers contained in this book have been modified as per the experts comments and also incorporate most of the important points that emerged during discussions. Each chapter is followed by the recommendations arrived at during the workshop.

We hope that the collection of these papers besides being useful to the members of the Academy, would also help in initiating a national debate on the subject with a view to find out the most suitable immunization strategy for our country with the ultimate aim of controlling the high incidence of communicable diseases.

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ACKNOWLEDGEMENTS

We are thankful to the Delhi Branch of Indian Academy of Pediatrics for providing an opportunity to organise the Workshop on Immunisation Practices in children. We are grateful to all the participants and the experts for their active involvement in the Workshop deliberations. Contributors to this volume deserve our greatful thanks for their untiring efforts. We are also thankful to the National Academy, particularly its President, Dr. D.G. Benakappa & Hony. Secy. Dr. R.D. Potdar for providing all the neccessary encouragements. We are also extremly thankful to different funding agencies which have helped us to organise the workshop.

— *Convenors*

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SUGGESTED IMMUNIZATION SCHEDULE

Birth	BCG	OPV*
6 Wks.	DPT	OPV
10 Wks.	DPT	OPV
14 Wks.	DPT	OPV
9 months	Measles	OPV*
18-24 months	DPT	OPV
2-3 yrs	Typhoid	Two Doses At one month interval
4-6 yrs.	DPT/DT	

* Optional but preferrable.

SUGGESTED IMMUNIZATION SCHEDULE FOR UNIMMUNIZED 1 TO 5 YRS OLD.

1st Visit	B.C.G., DPT, O.P.V.
1 month later	D.P.T., OPV,
2 months later	Measles, DPT, OPV,
1 year after last visit	DPT, OPV,
2-3 Yrs	Typhoid (Two Doses at one month interval)

B C G 1

G.R. Sethi

EXTENT OF PROBLEM

Tuberculosis continues to be a major health problem in India. Nearly 1.8% of the population above 5 years of age is suffering from radiologically active pulmonary tuberculosis of which about one fourth are sputum positive or infectious. 2.8% of children less than 5 years and 13.4% of children 5-9 years are infected with tubercle bacilli. Annual attack rate of infection (per thousand) is 8, 11 and 20 in the age groups 0-4, 5-9 and 10-14 years respectively. The mortality rate is 80/100,000 and it is the single largest killer causing 500,000 deaths/year (1). It is particularly fatal in children because of hematogenous spread at this age.

Human hosts have the ability to develop resistance to tuberculosis. The degree of resistance depends on natural as well as acquired factors. Acquired resistance may be developed naturally or artificially. The resistance acquired by natural exposure to virulent organisms is definitely effective. Unfortunately, unlike in many other infections the primary lesion of tuberculosis is a potential focus for the development of the active disease later (secondary tuberculosis) since it usually harbours viable bacilli in a dormant form. Moreover in some, the primary exposure in itself may lead to serious disease.

VACCINE

BCG vaccination is aimed at replacing natural and potentially harmful primary infection by a benign, artificial primary infection to stimulate acquired resistance against subsequent infection with virulent mycobacteria.

The protective effect of BCG vaccine against tuberculosis has been well demonstrated in animal experiments. Evidence of the protective effect in man, is however, conflicting.

BCG vaccine consists of living bacteria derived from an attenuated bovine strain of tubercle bacilli. The bacilli used for

vaccine production are descendants of the original Calmette strain of BCG. Due to different methods of maintenance in various vaccine production laboratories, many substrains have evolved during the last few decades.

The WHO recommends the 'Danish 1331' strain for production of BCG vaccine. Since 1967, the BCG laboratory Madras has been using the 'Danish 1331' strain for production of BCG vaccine. Emphasis has been laid on regular check up of quality of vaccine, at the International Reference Centre for BCG quality control at Copenhagen. Presently the vaccine available in the country is freeze dried, although earlier liquid vaccine was being manufactured.

Storage

Under refrigeration, liquid vaccine has a life of only 2 weeks. In contrast freeze dried vaccine can be kept at sub-zero (−20°C) temperature for 2 years and at 2°C to 8°C (i.e. in ordinary refrigerator) for 1 year. After reconstituting it with normal saline (distilled water being irritant, is not recommended) it must be used within 3 hours.

Efficacy

Children vaccinated with BCG develop hyper-sensitivity to tubercular proteins as demonstrable by intradermal PPD testing. Whether this represents development of immunity to tubercular infection is a matter of debate. At best only 70% of children receiving B.C.G. at birth, show tuberculin conversion. However many children who do not show tuberculin conversion, demonstrate evidence of cell mediated immunity (CMI) against tubercular protein as evidenced by lymphoblast transformation test (2). Tests like Soluble antigen flourcent antibody (SAFA) and Enzyme linked immunosorbent assay (ELISA) for humoral antibodies against tubercular proteins have been recently used for diagnosing tubercular infection (3, 4). However the effect of BCG on these tests has not been elucidated so far. The real proof of BCG efficacy in preventing the disease would essentially have to come from carefully controlled field trials.

Table I — Efficacy of BCG Vaccination

	Author	Period	Age	Duration of Follow up (years)	Protective efficacy (%)
1.	Aronson et al (North America)	1935-38	0-20 years	9-11	80
2.	Rosenthal et al (Chicago)	1937	3 months	12-23	75
3.	Comstock et al (Georgia)	1947	6-17	20	0
4.	Bettag et al (Illinos)	1947-48	Adoles-cents	12	0
5.	Palmer et al (Puerto Rico)	1949-51	1-18 years	5½-7½	31
6.	Comstock et al (Georgia)	1950	5 years	14	14
7.	British Medical Research council (Uganda)	1950-52	14-15½	15	78
8.	Moller et al (South India)	1950-55	All ages	2-7 upto 14	60 31
9.	Collaboration of ICMR, WHO and U.S. Public Health (South India)	1968-76	All ages except in-fants less than one month	7½	0

Numerous trials (5-10) have been conducted in different parts of the world. Most reports are uniformly favourable but some have instilled doubts about the usefulness of BCG (Table I). The protective value in these studies shows a wide variation (0-80%).

Earlier results in the Chingleput trial had shown no protection against sputum positive adult type of tuberculosis (10). However follow up of BCG vaccinated children for evidence of protection against childhood tuberculosis has given interesting results. Among children followed for five years or less, no protective effect against pulmonary tuberculosis was seen. However among those followed from 5 to 12½ years, about 50% were protected against pulmonary tuberculosis (11, 12).

After the Chingleput trial, WHO study group recommended that BCG vaccination of young infants should be continued, as data on childhood tuberculosis was still scarce. It suggested diagnostic criteria for childhood tuberculosis and initiated a global evaluation programme comprising case control and contact studies. A study of later type was conducted in Lome, using the scoring system recommended by WHO for the diagnosis of childhood tuberculosis (Table II). The study was carried out from September 1983 to November 1985 to evaluate the effectiveness of BCG vaccination of the newborn in an African community (13).

This study confirms that a programme of BCG vaccination in the newborn conferred over 60% protection against all types of childhood tuberculosis. Another trial (14) at Cameroon has shown 66% protection against pulmonary tuberculosis in young adults. Similarly a case contact study from Bangkok has shown 53% efficacy of BCG (15)

Table II—WHO Scoring system for diagnosing childhood tuberculosis

Features	Score
Chronic cough	+ 1
Meningeal signs	+ 1
Matted peripheral lymphnodes	+ 3
Hilar adenitis	+ 3
Infiltration with cavity	+ 4
Miliary Shadows in Chest X-ray	+ 4
Erosion of one or more vertebrae	+ 3
Positive culture of laryngeal swabs or lymphnode aspirate	+ 7

Features	Score
Rapid response to Antibiotics	− 6
Radiological improvement without ATT	− 3
and with A.T.T.	+ 3

Note : Children of Score 6 or higher are considered as cases of tuberculosis.

Routine BCG immunization has been stopped in Sweden on April 1, 1975. The annual incidence of tuberculosis per 100,000 children(0-4 years)increased from an average of 1.1 case in the period 1970-1975 to 1.3 cases in the period 1975-1979 and 2.1 cases in the period 1980-1984. The protective efficacy of BCG vaccination against childhood tuberculosis was estimated to be 85% (16).

Effectiveness of BCG vaccination has been studied three times since the inception of programme to give BCG at the age of 13 years in England and Wales. The protective value (75%) of BCG has remained unchanged from 1953 to 1983 (17). Retrospective analysis of hospital data (18) has shown that incidence of tuberculosis is less in BCG vaccinated. Occurrence of miliary tuberculosis and other manifestations of disseminated tuberculosis as well as mortality are also less in vaccinated. Prospective studies on vaccinated children in contact with active infectious cases showed similar results (19). A hospital based study (20) also suggests that BCG protects against hematogenous spread of disease.

It can be summarised from above that there is enough evidence to suggest that neonatal BCG offers at least 50 to 60% protection against childhood tuberculosis, more so against its disseminated forms and hence it must be continued in national health programme. There is of course, a great need to collect more data on this issue as also to develop better strains of vaccines.

Age of Vaccination

Although some studies have shown a slightly higher tuberculin conversion rates when BCG is given at 3 months of age (21) most studies have shown good sensitization even when BCG was given at birth (22). BCG has been found to be effective in preterm infants also (23). Therefore the current practice of giving BCG at birth is to be continued especially in view of high endemicity of the disease in our country.

Dose

The standard dose of BCG vaccine is 0.1 mg in 0.1 ml volume. The recommendation of reduced dose (0.05 mg in 0.05 ml) in the first month of life is without any scientific basis. Hence a standard dose of 0.1 ml is recommended at all ages using a tuberculin syringe fitted with 26 gauge intradermal needle.

Technique

Various steps in the administration of BCG include, opening of ampoule, reconstitution of freeze dried vaccine, filling of syringe, and intradermal injection with required volume of vaccine. Meticulous attention is required at each step.

If a freeze dried vaccine is opened without a plastic sheet, a rush of air into the ampoule on release of vaccum, can result in blowing out part of the vaccine powder. Excess of fluid during reconstitution may decrease the numbr of live organisms per dose. If the fine haze of vaccine powder along the walls of the ampoule is not carefully drained down with fluid, similar results are seen. In mass campaigns, the needle is often passed through a naked flame for its sterilization. The organisms contained in the length of the needle are killed. This practice is to be strongly condemned and use of separate disposable or reusable autoclaved needle, must be adhered to for every case. In mass campaigns jet injections may be useful for BCG administration (24).

Re-vaccination

Seth et al (2) studied cell mediated immunity (CMI) in children 1 -

6 years of age who were vaccinated at birth. The study revealed that the tuberculin test was positive in only 38.7% at 1 year and in 26.5% at 6 years, but the change in CMI was not so much when tested by the Leucocyte migration inhibition test (LMIT). LMIT positivity was 54.8% at 1 year and there was no further decrease in prevalence of positive LMIT after 1 year. The results show that a waning tuberculin test does not necessarily mean an absent CMI to tubercular protein. Spirer et al (25) demonstrated that phytahemagglutinin (PHA) transformation could be evoked even among children at adolescence who had received BCG at birth. Further investigations are necessary to find out a parameter of CMI which could indicate the presence or absence of immune response and the need for revaccination if any. Currently available data does not indicate the necessity of revaccination.

BCG IN NATIONAL IMMUNIZATION PROGRAMME

UIP emphasises that BCG vaccination should cover 85% of children under 1 year of age by 1990. Achievement of this target is nothing but a pipe dream in view of the recently published WHO Weekly Epidemiological Report (26) which shows that only 29% infants are currently covered under UIP. There is obviously a great need to expedite the coverage if the targets have to be met. It will be important to train the Multipurpose workers, Health assistants and General duty Medical officers in the technique of intradermal injection so that they can participate in vaccination programme. Also it is important to step up the supply of BCG vaccine to maintain a constant availability. Smaller dose ampoules may also help in increasing the coverage and reducing the wastage.

PROSPECTIVE VACCINES (21)

Various fractions of tubercle bacilli have been utilised to develop vaccine against tuberculosis. These include Ribbs' cell wall vaccine and Youman's so-called ribosomal vaccine. None of them is better, safer or cheaper than BCG to warrant extensive clinical trials.

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Recommendations

1. BCG vaccine should continue in the National Health Programme.
2. It should be given at birth or at the earliest contact thereafter.
3. Revaccination is not recommended.
4. All categories of health workers involved in UIP should be trained in the technique of intra-dermal injections.
5. A standard dose of 0.1 ml should be given at all ages.
6. Those children who do not show any reaction within 3 months of BCG vaccination should be given revaccination (if possible after tuberculin testing).
7. A separate needle should be used for every child. In any case sterlisation of needles by flaming should not be done.

Areas of Further Research

1. Assessment of BCG efficacy by carefully planned studies incorporating WHO criteria of disease definition and case contact methods.
2. Search should continue for better vaccine against tuberculosis.

Diphtheria, Pertussis & Tetanus

2

B.K. Sharma & P Choudhury

D.P.T. or Triple antigen has been available for clinical use since early twenties. There is definite evidence that its wide spread use has resulted in dramatic decline in the incidence of the three diseases in the developed countries (1). Because of this, many countries especially, UK, Japan etc. discontinued routine pertussis immunization which only resulted in the resurgence of the disease forcing them to restore pertussis immunization programme (2-4).

In India DPT immunization has been a part of EPI since 1978. Its use has been stepped up under the UIP. There has been a significant increase in the number of doses of DPT being administered annually in our country (Table I). Even then the total number of doses administered represent only 25% of potential 44 millions (Under twos) beneficiaries (1, 5). Independent surveys have also shown a dismal picture with only 0.6 to 25% coverage in rural areas and 12-54% coverage in urban areas (Table II). (6-13).

MAGNITUDE OF THE PROBLEM

Dismal performance on immunization front is also reflected in the continuing high incidence of these diseases in our country. The 1981 sample survey showed that 0.23 to 0.25 million infants died of neonatal tetanus. The reported incidence varied from 10 to 20 per thousand live births. Additionally over 50,000 cases of tetanus occur annually in older children and adults (14).

The annual reported incidence of diphtheria has varied from 15,000 to 35,000 with an average of 25,000 cases (14). Although Madras registered some decline (15), but the same has not been the experience at Infectious Diseases Hospital (Delhi). The incidence of diphtheria and tetanus as reported from various hospitals of Delhi is shown in Table III (16).

It is most difficult to estimate the incidence of pertussis because of ill defined symptomatology and poor reporting. Nevertheless

Table I — Year wise Reported Vaccination Performance

Vaccine	No. of Beneficiaries in Million			
	80-81	81-82	82-83	83-84
DPT	7.15	9.23	10.14	10.91
DT	10.23	10.81	10.23	12.41

Table II — DPT Immunization status of Preschool children.

Area	Year	Urban/Rural	Percentage
Delhi (6)	1972	Rural	0.6
Jabalpur (7)	1975	Urban	11.9
Kerela (8)	1976	Rural	25.0
Delhi (9)	1976	Urban	54.8
Kerala (10)	1976	Rural	12.0
J & K (11)	1977	Rural	1.0
Rajasthan (12)	1981	ICDS	44.2
Jabalpur (13)	1982	Urban	44.0

nearly 3,00,000 cases are reported annually. Almost 80% unimmunized persons contract the disease with a case fatality rate of 15 per 1000 (14).

VACCINES — The composition of DPT manufactured by different organisations is shown in table IV against WHO recommendations for the same. The vaccines available (TT, DT, DPT) are aluminium phosphate adsorbed. Td, a vaccine for use in older children is not available in the country, but can be made by mixing 0.1 ml of DT with 0.9 ml of TT just before injecting the same.

Table III — Incidence of Diphtheria and tetanus in Delhi hospitals (1978-88)

Year	DIPHTHERIA ID Hospital		TETANUS KSC Hospital (< 12 yrs)		TETANUS LNJPN Hosp, (< 12 yrs)	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
1978	278	42	483	287	502	223
1979	165	23	386	262	426	205
1980	164	33	349	208	438	238
1981	183	40	481	313	419	182
1982	237	51	551	302	408	187
1983	247	49	730	480	493	261
1984	236	48	480	296	296	102
1985	261	66	525	290	386	197
1986	272	66	508	281	404	139
1987	273	71	365	221	292	85
1988	284	93	308	221	—	—
	(Upto Sept)		(Till Aug)			

Vaccine production in India India is self sufficient in production of all the three (DPT, DT & TT) vaccines (5). It is proposed to step up the production of these vaccines to meet the increased requirements under the UIP programme (Table V)

Storage & Transport of DPT

All tetanus containing vaccines (DPT, DT & TT) are tne least heat labile vaccines that have been included in the EPI Programme. These vaccines should be stored at 2°C to 8°C and **should never be frozen.**

Table IV — Composition of DPT (per ml).

	CRI (Kasauli)	Glaxo	Bengal Immunity	Recommended WHO
DPT				
D. Toxoid	30 Lf.	50 Lf.	30 Lf.	20-50 Lf.
T. Toxoid	10 Lf.	10 Lf.	3-4 Lf.	> 10 Lf.
Pertussis (million)	32,000	40,000	20,000 mil	40,000
DT				
D. Toxoid	50 Lf.	—	—	20-50 Lf.
T. Toxoid	10 Lf.	—	—	> 20 Lf.
Td				
D. Toxoid	—	—	—	4 Lf.
T. Toxoid	—	—	—	20 Lf.

Table V — DPT Production in India (in Million Doses)

Public Sector	Present Capacity	2000 AD
C.R.I. Kasauli	13	18
Pasteur Inst. Coonor	7.5	15
Haffkine, Bombay	7	10

Schedule for immunization

Earlier the EPI committee of Government of India suggested a 5 dose (3, 4, 5, 18 months and 4 years) schedule of DPT. Similar recommendations were also received from EPI Global Advisory Committee of WHO. Recently however, both the Global Advisory

Committee (1) and the Government of India have advanced the age of first immunization to 6 weeks of age. Besides, the Government of India has also issued instructions for discontinuing of second booster of DPT between 4-6 years of age and instead to give only DT vaccine at that time. In fact instructions have been issued not to give DPT beyond 2 years of age and if a child presents to the health services for the first time after 2 years of age, it is recommended to give only two doses of DT instead of three doses of DPT as advised earlier.

Let us examine the scientific validity of these recommendations.

Age at First vaccination Neonatal susceptibility is determined by level of antibody titres transmitted from the mother (17). For almost all these diseases there is very poor transfer of immunity from the mother and even neonates are susceptible (18, 19). Unless mother is immunized in pregnancy, incidence of neonatal tetanus is high and it continues to be a major cause of mortality in our country. Although maternal antibodies against pertussis are found in infants, they offer hardly any protection and even neonates are susceptible to pertussis. In fact the case fatality rate with pertussis is highest in first 6 months of life. Thus there is a great need to complete the 3 dose primary schedule of DPT by 6 months of age (20).

The response to diphtheria toxoid and tetanus toxoid (in the absence of any transplacental immunity) is good even when given in the first week of life. However response to pertussis vaccine is seen only in 12-23%, when given in first 15 days of life. Even at 4 weeks, seroconversion seen with pertussis vaccine is poor (21, 22, 23).

Reasons for this poor response to early pertussis immunization are not well understood as it does not correlate with the levels of maternal antibodies present in the infant. In one study seroconversion after 3 doses of DPT given at 2, 4 & 6 months of age was poorer in a group of children who had also received an additional dose of vaccine at less than 4 weeks (mean 3½ days) of age (21). Thus it would appear that vaccination earlier than 4 weeks is not advisable and it is best to start the vaccination at 6-8 weeks of age to ensure completion of primary immunization by 6 months of age.

Second booster at 4 to 6 year of age, DPT or DT ?

Three basic considerations will help to decide whether the second booster at 4-6 year of age should contain pertussis component :

a) **Incidence of pertussis after 4 year of age** — Although no reliable age-wise data is available in our country, yet it is clear from every day experience that the disease is fairly common in older children and even in adults. In fact these children, although suffering from mild disease themselves, help to spread the infection to susceptible infants in the community (20).

In USA, 53% reported illness for pertussis occured among children under 1 year of age. As many as 22% cases occured above 5 years of age (20).

b) **Duration of protection offered by 4 doses of DPT given by 18 months of age** — Antibody levels following the 4th primary (or the first booster) at 18 months of age progressively decline. In areas of low endemicity like USA & UK because of absence of natural infection, these children become susceptible after 4 or 5 years of age (20). It is possible that in areas of high endemicity like India, natural infections may keep boosting the antibody levels. However no definite data on persistence or otherwise of pertussis antibody levels beyond 4 year of age is available in our country, to warrant the discontinuance of the second booster of DPT.

c) **Fear of side effects** It has generally been said that the pertussis vaccination in older children is associated with more frequent & severe side effects. This in fact is not true. At least two studies, one conducted in pregnant mothers (24) and the other in adult male volunteers (25) have not shown any increased frequency of adverse reactions except for mildly increased local reactions. However, the potential side effects of DPT beyond 6 years of age outweigh the possible benefits and hence it has generally been recommended that pertussis vaccine should not routinely be given to children beyond 6 years of age (20). Considering all the above factors, it is imperative that second

booster of DPT continues in the national immunization schedule so as to prevent the occurrence of pertussis infection in older children and young adults who could act as source of infections to infants.

Vaccination to Unimmunized child older than 2 years of age :

Children above 2 years of age remain susceptible to pertussis and in fact the highest attack rate of pertussis are seen in 1-4 years olds (20). The reaction rates of DPT are not unduly increased after two years of age. Immunization practices advisory committee (USA) recommends (20) routine immunization of all children with 5 doses (3 primary and boosters at 18 months and at school entry) upto 6 years of age. Second booster is not required only if the first booster itself has been given after 4 years of age. Adding pertussis component to DT does not entail any additional significant cost. For DPT, 3 primary doses would be required at intervals of 4-6 weeks even in older children and this should be given to all children upto 6 years of age who have not been immunised earlier. It is only after 6 year of age that pertussis vaccine is not required.

Interval between consecutive doses

There is evidence that better seroconversion is provided if the interval between consecutive doses in 6 months or so. In fact if first two doses are given 6 months apart than seroconversion is so good that a third dose may not be required (26, 27). Practical difficulty of increased dropouts because of longer intervals, and the need of providingcomplete protection against pertussis in the crucial first 6 months of life, precludes the utility of this 2 dose-long interval-schedule (28). Indian experience is that the drop out rate is as much as 20 to 25% for the 3rd dose (29) and longer the time gap between successive doses, will be the drop out rate (1). Further, seroconversion following 3 doses at 1 month interval has also shown to be equally good (28). Intervals shorter than 4 weeks are not recommended as this leads to interference and poor development of antibodies. Considering all aspects of the problem, 1 month interval is most suitable for the 3 primary doses of DPT.

Primary immunization : 2 doses or 3 doses ?

As mentioned above 2 doses given 6 months apart give adequate protection against all the three diseases, but when they are given 1 month apart, protection provided is much less esp. against pertussis. Antibody levels which developed, after 2 doses of DPT were borderline against diphtheia in 35%, pertussis in 68% and tetanus in 1% children and could be expected to wane away rather quickly (30). Thus to ensure complete and longer lasting immunity, it is important to give 3 primary doses of DPT (30, 31).

Side effects of DPT Majority of adverse reactions seen with DPT injection occur because of pertussis component although local reactions and mild systemic side effects like fever, malaise can occur with DT injection also. In older children & adults even convulsions can occur with DT and that is why Td (one tenth amount of diphtheria toxoid as in DT) is advised in them (20).

Frequency of various side effects occuring with DPT is shown in Table VI. Severe side effects will warrant discontinuance of further doses of DPT (20, 32).

Table VI – Reactions to DPT (20)

(Figures in parenthesis indicate incidence)
Local (30-50%)
Redness, Swelling, Pain
Systemic
Mild (20-50%)
Fever, Irritability
Anorexia, Drowsiness
Severe
Persistent Crying, High Fever (<1%)
Hypotonic-Hyporesponsive State,
Convulsions (<0.1%)
Encephalopathy (1/110,000)
Neurological Deficit (1/310,000)

Why is Pertussis vaccine toxic Presently available pertussis vaccine is a whole cell vaccine which contains many antigenic components which are both toxigenic and immunogenic. This vaccine contains Lymphocyte promoting factor (LPF) and Filamentous haemagglutination factor (FHA) besides other antigens. Most of the reactions to pertussis vaccine are believed to be due to the LPF antigen (33, 34). Efforts are on to make newer acellular vaccines which contain the immunogenic components but are devoid of toxigenic components. A monocomponent (LPF or FHA) and a bicomponent (LPF, FHA or other toxins) acellular vaccine have been manufactured and tried in Japan and Sweden. Although earlier studies done in Japan showed very encouraging results (35), but later studies in Sweden have shown a protective efficacy of only 66% with these types of vaccines (34). Clinical trials are still going on and we may hear more about these vaccines in near future (34-36).

Deaths due to DPT A few deaths have been reported both in India and abroad (34) after administration of DPT vaccine. But detailed investigations have revealed that in none of these cases, could death be attributed to DPT vaccine itself. It has been traced to either administration of wrong injection (Like scoline instead of DPT) or to bacterial contamination of DPT because of repeated withdrawal of vaccine from the vial without observing basic aseptic precautions. Some deaths have been attributed to the simultaneous occurrence of pneumococcal or hemophillus influenzae bacteremia in the infant which had not been detected at the time of DPT administration (34, 36).

Contraindications to DPT

DPT is contraindicated only in infants with progressive neurological disease or with uncontrolled seizures. Stable neurological conditions like cerebral palsy and developmental delays are not considered contraindications for DPT immunization (Table VII). It will be prudent to postpone vaccination of infants with early catarrhal symptoms like fever, cold, cough etc, as it could represent the prodromal stage of very many illnesses, course of which could be complicated by the side effects DPT vaccine. Children who have continued running nose or cough (most often allergic in nature) should not be denied vaccination.

Children who experience severe reactions (Table VI) with first dose of DPT should also not be given further doses of DPT. They should instead be given DT injection.

Table VII — Contraindications to Pertussis

None

Mild URI, Diarrhea
H/o Symptomatic seizures
Short term steroids
Family history of seizures

Relative

Fabrile seizures
Epilepsy

Absolute

Progressive neurological disease
Severe reactions to previous dose.

DPT in malnourished children Several studies have documented adequate seroconversion following 3 doses of DPT vaccine even in severely malnourished children and hence these children should be vaccinated just like their normal counterparts (27, 31, 37).

DPT in Preterm & Low Birth Weights

Seroconversion in preterm infants following DPT immunization beginning 6 weeks of age is also adequate and hence these infants can also be immunized just like the term infants (38-40)

DT & TT in older children & adults

Because of its higher content of diphtheria toxoid (30 to 40 Lf) DT is not recommended after 6-7 years of age as it may cause

unwarranted reactions including convulsions. After 2nd booster of DPT given between 4-6 years of age, it is recommended to give one booster of Td at 12-14 years of age and then a tetanus toxoid every ten years. More frequent boosters of TT are not necessary and may be associated with higher rates of side effects (20).

TT in pregnant mothers — Unimmunized mothers should receive at least 2 doses of tetanus toxoid beginning anytime after the first trimester of pregnancy. The two doses should not be given at less than one month interval and the second dose should be given at least 15 days prior to the date of delivery (40). In subsequent pregnancies, only one dose of tetanus toxoid given any time during 2nd or 3rd trimester is adequate. Recently few trials have been conducted using single dose TT containing higher amounts of tetanus toxoid even in previously unimmunized people (42-44). Optimal dose of TT and optimal timing of single dose during pregnancy is still not clear (45).

Table VIII—Tetanus prophylaxis in wound management

	Nature of Wound	
	Clean	Contaminated
Unimmunized or Incompletely immunized or Lapse of 5 years since last dose of TT	TT*	TT + TIG**
Completely Immunized with a booster within last 5 years.	Nil	T I G**

* DT or DPT if child < 5 years of age. Complete the immunization schedule thereafter.

** TIG (Tetanus Immunoglobulin) dose 250-500 I.V./I.M.

Tetanus prophylaxis in wound management

Table VIII gives the guidelines for tetanus prophylaxis depending on the immunization status and the type of wound. If immunization status is not known the person should be treated as an unimmunized individual.

Immunity after an attack of disease

An attack of diphtheria or tetanus does not give lasting immunity and hence active immunization should be initiated against these diseases at the time of discharge. On the other hand confirmed case of pertussis need not be given pertussis vaccine.

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Recommendations

1. Three doses of DPT for primary immunisation should continue. The vaccination should start at 6-8 weeks and given at 4-6 weeks interval.
2. There is no need to restart the series irrespective of the time elapsed between successive doses.
3. First booster should be given 1 year after the third primary dose.
4. Second booster of DPT/DT should be given at 4-6 years of age.
5. Only absolute contraindications to DPT are :
   a) Progressive neurological disorders
   b) Severe reactions after the first dose

Areas of Further Research

1. Epidemiological data on occurrence of pertussis at different ages.
2. Longitudinal studies of levels of antibodies to different components of DPT and occurrence of disease after first booster only.

Poliomyelitis 3

Siddhartha Sen

INTRODUCTION

To state that poliomyelitis is an important public health problem in India would be an understatement. It continues to be a potent threat to life and limb among the vulnerable population. Though the mortality is not very large, the morbidity it causes is devastating : those that survive the disease have to go through life with the stigma of a deformed and maimed limb. The situation is rendered even more poignant by the fact that poliomyelitis almost invariably effects the innocent young, from the under privileged, overworked classes. The economic implications of a physical handicap in a member of the working class are obvious.

MAGNITUDE OF THE PROBLEM IN INDIA (1-8)

No authentic data regarding the incidence of poliomyelitis in India is available, but most hospital and survey based data tend to show that the incidence of the disease has not decreased significantly over the past 10 years. Figures from the Central Bureau of Health Intelligence is presented in Table 1. These probably represent only a small fraction of cases as surveys conducted in 1981 and 82 showed that actual number of cases are at least 10-15 times higher than the reported numbers. Estimates put the annual incidence of polio in India to be between 200,000 to 300,000 cases per year (5-7), which means that 500-700 cases occur every day or one child is afflicted every 2 minutes by this disease (8).

Data from different metropolitan cities (1, 2, 4, 5) are presented in Table II. These also clearly show that there is no decline in the incidence of disease at these centres also. Better reporting and increasing population size can only partly account for the large number of cases seen in 1987.

Table I — No. of cases of Poliomyelitis reported (Central Bureau of Health Intelligence)

Year	Number	Year	Number
1975	13,000	1981	28,709
1976	13,711	1982	21,469
1977	12,482	1983	21,310
1978	15,670	1984	18,042
1979	17,229	1985	18,458
1980	16,685	1986	16,550
		1987	19,617

Table II—No. of Cases of Acute Polio Seen at Various Centres of India Over the Years

	Bombay	Calcutta	Madras	Delhi
1975	—	1243	569	1288
1976	—	1565	633	963
1977	—	1309	625	1335
1978	—	1798	638	1805
1979	—	2382	626	1715
1980	1366	2159	887	2000
1981	1226	2120	1685	2090
1982	1458	2302	1320	1646
1983	1282	1871	1158	1565
1984	1300	2169	895	1550
1985	1503	—	1268	1451
1986	1702	—	—	1452
1987	1379	—	—	1874
1988 (upto Sept)	—	—	—	2702

BOMBAY : Enterovirus Research Centre (1, 2)
CALCUTTA : B.C. Roy Polio Clinic & Hospital for Crippled children. (4)
MADRAS : Institute of Child Health & Hospital for Children (5)
DELHI : Kalawati Saran Children's Hospital.

VACCINES AGAINST POLIOMYELITIS

For the control of poliomyelitis, two potent and effective vaccines are available : the oral poliovaccine (OPV) and the inactivated polio vaccine (IPV). Both these vaccines, used correctly and intelligently have shown dramatic results. In Sweden (9) and Finland (10) where only IPV is used, polio has disappeared. In the United States (11) and Great Britain (12) similar results have been shown with OPV. Even in some third world countries like Cuba, Brazil and Chile (13) poliomyelitis has been largely controlled by the intelligent use of OPV. In some regions like the Gaza strip and West Bank (14) combined use of OPV and IPV have yielded extremely gratifying results.

ORAL POLIO VACCINE

Oral polio vaccine is prepared from live attenuated strains of the three types of polio viruses. Subcultures of the original Sabin strain are still in use. Since the early 1960's only trivalent OPV has been used in India. The standard trivalent OPV contains type 1 : 10^6 TCID 50, type 2 : 10^5 TCID 10 and type : 10^5 TCID 50 of viruses.

The vaccine used in India is thermostabilized by the addition of magnesium chloride. The shelf life of OPV is 4 months if stored at 2-8°C and 2 years if stored at —20°C (15). The vaccine is not manufactured indegenously and all the vaccine is imported at present.

OPV was introduced in the National Immunization Programme in 1978 and implementation was started in 1979-80. By 1984-85 only about 20% of under two's had received 3 doses of OPV, the coverage falling far short of the EPI target of 45% infants under one year of age (16). The current coverage with 3 doses of OPV is estimated between 30% (17) to 45% (18). In Delhi according to a recent survey conducted by the Delhi Administration, the coverage for 3 doses of OPV was between 55% to 92% (19). Greater Bombay too has achieved 50-60% coverage (5). However incidence of disease even in these cities has not shown any decline as shown earlier (Table II).

PROBLEMS WITH OPV IN INDIA

One of the main problems of OPV in India is the inadequate seroconversion (20-23) seen after 3 properly spaced doses of OPV (Table III). Seroconversion is better after 5 or 6 doses (23, 24). This problem is not unique to India but is seen in almost all tropical developing countries with poor levels of hygiene and sanitation (25, 26). In India and other developing countries, the proportion of children immunized after 3 doses of fully potent OPV equals approximately the proportion of children immunized after 1 dose in the United States (8). Many reasons like immunological immaturity of infants (27), interference by other enteroviruses in the gut (28), loss of potency of the vaccine and interference with maternal antibodies in breast milk have been cited from time to time, but all these have been disproved as the cause of low rates of seroconversion (22, 29).

Table III—Seroconversions after OPV (%)

	Type 1	Type 2	Type 3
3 Doses of OPV			
Ghosh et al (20)	40	74.7	56.6
Chaudhary et al (21)	63.4	74.6	67.6
Idris et al (22)	77.6	76	37.5
Jhala et al (23)	77	72	56.3
5 Doses of OPV			
John TJ (24)	83	96	82
6 Doses of OPV			
Jhala et al (23)	100	87	87

Another problem with the use of OPV in India is the break in the cold chain, which renders the vaccine impotent. Oral polio vaccine being very thermolabile ; even with the use of ice lined refrigerators, walk in coolers and ice-packed vaccine carriers, we

seem to have achieved very little. In 1986 it was found that in Maharastra only 48% of the OPV samples randomly checked were potent (3). Between January 1987 to March 1988, of the 337 samples tested from all over the country, only 154 (45.7%) were found to be potent (30).

NUMBER OF DOSES AND AGE FOR VACCINATION

It is seen that as the number of doses is increased from 3 to 5, the seroconversion rises. Jacob John (8) states that if all children receive 5 doses of potent OPV, 90-95% will be protected and if they receive 6-7 doses, 95-99% of them will be protected. For an individual child, advocating 5 or more doses is probably correct, but advocating this as a national policy is impractical and inadvisable for a number of reasons :

1. Non availability of such large number of doses of OPV.
2. High drop out rates. It has been seen that between any two dose of vaccination, there is a drop out rate of 25-30% (31), which means that of an original 100 children who receive the first dose, only 32 will complete the 5th.

The World Health Organisation at the seventh meeting of the Expanded Programme on Immunization Global Advisory Group in 1984 recommended (32, 33) 4-5 doses of OPV for developing countries (Table IV).

Table IV—O.P.V. in developing countries : WHO Recommendations (1984)

Birth	OPV, BCG
6 wks	OPV, DPT
10 wks	OPV, DPT
14 wks	OPV, DPT
9 m	Measles,OPV*

* for countries where seroconversion rates after 4 doses are inadequate.

The idea of giving OPV at birth is that 70-100% neonates benefit by developing local immunity in the intestinal tract and in addition 30-50% develop antibodies to one or more poliovirus types (34). Moreover, no harmful effects have been observed by vaccinating neonates. There is no evidence of immune tolerance induced by early immunization. Infants who fail to respond with serum antibodies following immunization in the neonatal period respond normally to subsequent doses of the vaccine (34).

In a recent editorial comment, Dr. Jacob John ratified the above schedule, and advocated it for the National Immunization Programme (35). What he particularly appreciated was that each dose of OPV was conveniently 'piggybacked' with another vaccine. Although theoritically, this schedule seems to be quite attractive and practical,but it is not yet known if even this would succeed in our country with the dismal state of affair regarding cold chain maintenance. Also in a country like ours where 3 dose coverage for every child remains unfulfilled, 5 dose coverage would be unthinkable.

TARGETS IN INDIA

According to EPI/UIP targets, 85% of infants under 1 year of age should receive 3 doses of OPV by 1990. It is highly unlikely that this target will be achieved. But the crucial question is that even if such a target is achieved, can poliomyelitis be controlled in India by such a plan ?

For the control of a communicable disease like poliomyelitis, the rate of vaccination coverage should exceed the rate of natural infection (8). It is estimated that in India 50% children are naturally infected with poliovirus by 12 months of age, about 75-80% by 24 months of age and 90-95% by 36 months of age. Thus, for poliomyelitis control, vaccination rates should be much higher than these rates of natural infection (8). If about 75-80% under ones are immunized (as opposed to vaccinated) poliomyelitis may theoretically be controlled. To give protection to 75-80% of under-ones, 100% coverage of under-ones is required because of inherent low seroconversion rates by OPV. The UIP target of 85% coverage of under-ones by 1990 will protect only about 64% of the under one population, provided that fully potent vaccines are used and targets are achieved. If vaccine used have

the current level of potency, the UIP target will manage to protect only about 32% of the under-one population, and poliomyelitis will continue and remain a major public health problem.

Even if high rates of vaccination with fully potent vaccines are achieved, it is not sure if poliomyelitis can be controlled in India by routine 3 dose vaccination. High rates of OPV coverage have been achieved in Bombay (2), Delhi (19) and Madras (36) but large number of cases continue to be reported from all these cities.

A very revealing report from Gaza, a tropical region, puts grave doubt on the assumption that poliomyelitis can be removed by 3 doses of OPV as envisaged by the UIP. In this region, routine vaccination with 3 doses of OPV was practiced during 1967-1973 and 70% vaccination coverage was achieved. The incidence of poliomyelitis dropped by 33% (14). From 1973-1977 the vaccination coverage was increased to more than 90%, but there was no further decrease in the incidence of the disease. An extremely interesting feature was that the incidence of the disease increased in the vaccinated population from 34.6% in 1974 to 61% in 1977. In this region, it was clearly shown that the percentage coverage was high enough and the vaccine used was demonstrably potent. From 1978-1982 a new schedule was adopted incorporating both OPV and IPV following which the incidence of the disease dropped to one-fourth and in 1981-82, only 3 cases were seen. The incidence of disease among the vaccinated completely disappeared.

Similarly, cases of 'vaccination failure' or paralytic disease among the vaccinated children has been shown to be rising all over the country (1, 6). This could be ascribed to higher vaccination coverage only if the number of total cases showed a corresponding decline. But this has not been the case, and 'vaccination failures' appear to be out of proportion to the vaccination coverage.

ALTERNATIVE STRATEGIES

Should then India wait for the next 10 (or possibly more) years to achieve a high vaccination coverage and hope for decline in the incidence of polio ?

In this regard what Dr. Albert Sabin, world authority on OPV has repeatedly been stressing (13, 26, 37),is extremely important. He states, "I submit that mere acceleration of what is being done now-even with modifications aimed at temporary increase in coverage-will not meet the challenge of protecting the world's children before economic development brings a higher standard of living and adequate health care to all. The extensive, year round dissemination of viruses in the poverty stricken tropical and sub-tropical countries with inadequate health services calls for a strategy that is different from that used successfully in economically developed temperate countries" (26). He advocated use of OPV in a pulse manner (37).

In pulse immunization very large number of susceptible population (nearly 100%) receive OPV in a very short time (1-2 days). This simultaneous feeding of the vaccine virus to the largest number of children in the shortest time, gives rise to a more extensive dissemination of excreted vaccine virus than that occurs during an epidemic of natural disease. The vaccine strains thus have an opportunity to displace the large number of wild viruses rapidly in the community; a result that cannot be achieved by routine, round the year, vaccination. The dissemination of vaccine strains excreted by the vaccinated children also, serve to infect and immunize children who were missed out in the campaign or who did not otherwise seroconvert.

To cite examples of the successful use of this technique in the control of poliomyelitis, the experiences in Cuba, the Dominican Republic and Brazil are revealing (37). The strategy of National Vaccination days 2 times a year 2 months apart was first tested in Cuba in 1962-63 and has been continuing annually since. The vaccinations were taken up on a war footing and 100% coverage was achieved in 1 day and repeated 2 months later. The results were dramatic.

For a long time it was thought that such massive campaigns could be carried out only in small communist countries, but in 1980, Brazil, a non-communist country of continental size and a population of 125 million (1/5th of India) proved to the world that with will and dedication such a project is possible.

Routine vaccination with OPV had been going on in Brazil for quite some time and by 1979, 51.4% of the under 1 population had received 3 doses of OPV, but a high number of cases of paralytic disease continued to be reported. In 1980, a pulse immunization campaign was started. 90,000 vaccination posts were set up and 3,20,000 community volunteers took part in the project. About 18 million children less than 5 years of age received OPV on the 2 days, 2 months apart. Nearly 100% coverage was achieved. The results of this campaign were extraordinary. The annual incidence of the disease fell from 10 per 100,000 to less than 1 per 100,000 (38). These campaigns were carried on yearly, and the incidence of the disease has remained low over the next 5 years.

Polio immunization had been irregular in Mexico since 1959. As in many other developing countries, the vaccine was misused, coverage achieved was often poor and the cold chain was inadequate. In 1972 a mass campaign reached 100% of the children less than 5 years age-2 doses 2 months apart were given (39). The number of cases fell from an annual average of 900 for the previous 5 years (1.9 per 100,000) to 221 cases (0.4 per 100,000) in 1973 and 1974. Unfortunately the strategy of mass vaccination was abandoned in favour of routine vaccination throughout the year, and incidence of polio increased once again with peaks in 1975, 1977 and 1979. By 1980 the health authorities were convinced to start a mass campaign once again. Because of economic constraints only 1 dose of monovalent (type 1) OPV could be given to about 80% of under 5 years. The result was dramatic. Incidence dropped from 1.2 per 100,000 (or 800 cases) to 0.3 per 100,000 (i.e. 200 cases). In 1982 after a further mass campaign the incidence fell to 0.14 per 100,000 (96 cases).

Paraguay had its first national vaccination campaign in September 1985. Previous to this, 99 cases were seen annually over the last 5 years. After 3 months of the campaign no further cases were seen till mid 1986 (26).

In India too, mass pulse campaigns have been tried on a small scale at Vellore (40) with very gratifying results. In Madras city a mass immunization campaign was carried out in 1985. The campaign succeeded in rapidly increasing the vaccine coverage to 94%, 88% and 72% for the 1st, 2nd and 3rd dose from 66%, 62% and 52% respectively (36).

Some of the criticisms against mass/pulse vaccination programme is the lack of sustainability of this massive effort year after year. Do we have the administrative and logistic ability to carry out such campaigns ? What would the cost be ? A country which has successfully organized a large number of elections taking the ballot boxes to the remotest areas, can certainly be relied upon to organise such a campaign. Even economically this may be more feasible as it will obviate the necessity of routine maintenance of cold chain. It has also been said that such a strategy might upset the already running UIP (41). On the other hand if polio immunization programme can be concentrated on for a few days each year, will it not allow the main programme to perform its functions better ? Will it also not heighten interest in immunization in general ?

If India is to persist with OPV, pulse immunization should be used and a begining can be made on an experimental basis in selected districts of the country. If such a strategy is considered impractical or unfeasible, then IPV may be the only other alternative.

INACTIVATED POLIO VACCINE

The killed polio vaccine also known as the Salk vaccine, is an inactivated vaccine containing all three serotypes. It is inactivated by formalin and has to be given by intramuscular injection.

It was first introduced in the U.S. in the mid-fifties and was in use for a number of years. It was replaced by the then more convenient OPV in the early sixties. The IPV then in use, fell into disrepute for a number of reasons (42) :

1. Multiple injections were required.
2. The immunological response was uncertain.
3. The duration of immunity was allegedly short lived.
4. Cases of vaccination failure were reported.
5. More expensive than OPV.

Since then, nearly all these doubts have been dispelled. Recent advances in production and standardization of IPV now make it possible to induce durable immunity with just one dose of a suitably standardized vaccination. A single dose of a vaccine

containing 40, 8 and 32 D-antigen units of type 1, 2 and 3 polio virus respectively administered to 6 month old infants was observed to induce antibody levels of 1 : 4 in more than 90% and immunological memory in all (43). Since protection against paralysis is associated with the presence of either type specific serum antibody or type specific immunological memory, and since immunological memory once induced is irreversible, then life long immunity to paralysis can be induced with a single dose of suitable standardized vaccine (43).

This long term immunity and immunological memory has been demonstrated by other workers as well (44). Salk (43) recommends that in countries where poliomyelitis occurs before 6 months of age,IPV can safely and effectively be given before this age. A repeat dose however is recommended at 6 months age (45). Even in developing countries, 2 doses of IPV has been found to result in 100% seroconversion (46).

The trivalent vaccine can be used alone or mixed with DPT vaccine with Aluminium phosphate as adjuvant. One of the major advantages of this vaccine is its stability at 4-10°C and even at higher temperatures. In addition, the stability may be improved further by the addition of 'Arildone' as stabilizer (46).

The practical use of IPV has been demonstrated effectively in developed countries like Sweden (9) and Finland (10). In the Gaza strip, a tropical region, IPV was used to eliminate poliomyelitis dramatically after routine OPV vaccination failed (14). In India too, IPV has been used on a limited scale and the results have been extremely gratifying. DPT incorporated IPV was used on a small community in the mid 1980's, and with a coverage of 35%, the incidence of the disease was reduced by 85% (6). In a trial on the seroconversion rates of IPV in India, it was reported that 2 doses at 2 and 4 months of age produced immunity in 90-100% recipients. Here too DPT-IPV was used (47). Thus, two injections, given early in life were able to protect the child from all four diseases. IPV appears to be a near ideal vaccine to be used under Indian circumstances, but it is widely believed that the cost of IPV is prohibitive (5). But dispassionate review

revealed that this is not so. Of late, new methods in technology have led to the production of IPV on an industrial scale and at economically acceptable costs. Replacement of primary monkey kidney cells by subcultured monkey kidney, Vero or human diploid cells as substrate for virus multiplication as well as the introduction of technique of cell cultures on the surface of micro-carriers has greatly enhanced vaccine yield (46, 48). In an elegantly reasoned article Martin (31) shows how the cost of DPT-IPV vaccine in an EPI programme would actually be less than the 3 dose OPV schedule. This is because of reduced 'contacts' and reduced expenditure on 'cold chain' etc.

If this reasoning and analysis is correct, then India should seriously consider the logistics of using IPV in the National Immunization campaign in due course and at least start this immediately on experimental basis in some areas.

In conclusion it can be stated that routine 3 dose coverage with OPV to 85% of the under 1 year population would take a longer time than that targeted by UIP India. Even when such a coverage is achieved, poliomyelitis is unlikely to be controlled in India by this method.

For control of polio it would be necessary to use either IPV or OPV in a pulse manner for reasons mentioned earlier.

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Recommendations

1. Oral polio vaccine will continue to be the main stay of polio immunization programme in India for the present.
2. All children should receive at least 3 doses of potent OPV (6, 10 & 14 weeks) with DPT. This is an essential requirement.
3. Wherever possible, additional doses may be administered with BCG during the first month and with measles vaccine at 9 months of age.
4. Another dose of OPV at the age of 18-24 months should be given.
5. Information regarding maintenance of cold chain at various levels should be urgently disseminated to all levels of health workers including the specialists and the teachers in the Deptt. of Pediatrics and SPM all over the country.
6. All levels of health workers (including practitioners) should undergo a reorientation training in essentials of cold chain maintenance before they are allowed to dispense heat labile vaccine like OPV.
7. Facilities for potency testing of the OPV should be more widely available and well publicised among not only the Govt. Sector but also the private practitioners. Results of vaccine potency testing should be made available more widely, together with corrective actions taken.

Areas of Further Research

1. The efficacy of present 3 dose schedule needs to be assessed carefully by clinical and serological studies.
2. The value and feasibility of additional doses of OPV at birth and at 9 months as suggested above should also be evaluated in controlled trials.
3. *Pulse immunisation* with OPV should urgently be tried on an experimental basis in at least 5-6 districts in various states and if found useful should be incorporated in the National Immunisation Programme.
4. Similarly *killed polio vaccine* either alone or combined with DPT, needs to be assessed by multicentric studies for its usefulness and practicability.

Measles 4

Shobha Cherian

EXTENT OF PROBLEM

Measles has the highest morbidity and mortality among all vaccine preventable illnesses (1). In 1984 more than 1.5 million children died of measles and its complications in less developed countries. The six EPI diseases together kill 10 children per minute and disable 10 more. Measles alone is responsible for 1/3rd of these deaths (2, 3).

In unvaccinated populations, virtually all children are infected and a large majority develop clinical measles (1, 4). The incidence of measles in the USA, UK and India is 10.2-128, 250 and 500-2000 per 100,000 population respectively (5-7).

In tropical countries between 15-30% cases of measles occur in children less than 12 months (3, 8, 9). In India 10-37% suffering from measles are under 1 year, 22-70% below 2 years and 80% below 3 years (1, 10-13). In developed countries the median age at which children suffer measles is 4-6 years (14) as compared to 1-2 years in India (1). In UK, 1% people with measles are hospitalised and one in 10,000 die. This is measles at its most benign (4). The case fatality rate (CFR) of measles in India has been reported between 1-3% and among survivors 30% suffer severe complications (11, 13, 15, 16). One study reports the CFR to be upto 16% in edpidemics (1). Overcrowding, protein energy malnutrition and young age may contribute to a CFR of upto 20-40% in developing countries (17). Ten percent of preschool deaths and 2% infant deaths in India, are caused by measles, making it the third most common cause of death in under fives. In other words, measles kills more than 200,000 under five children per year (1, 7, 18, 19). All this is despite the fact that we have a vaccine which is 95% effective.

TYPES OF VACCINE

Measles vaccine was first licenced for use in 1963. The various types of measles vaccines are listed in Table I (20). Measles vaccine is a freeze dried preparation containing a live attenuated

measles virus. The further attenuated Schwartz & Moraten vaccine virus strains are the most commonly used. For vaccine production, the virus is grown on chick embryo cell culture. The viral liquid culture is stabilized with sorbitol and gelatin and then lyophilized.

The Human Diploid Cell vaccine (HDC) and the Edmonston Zagreb Chick embryo fibroblast vaccine (E-Z, CEF) which has been passaged through human diploid cells have also been tried successfully. The higher seroconversion rates with these vaccines in younger infants (4-6 months of age), even those with higher maternal antibody titres, probably make them superior to the currently used Schwartz and Moraten Strain vaccines (21-23).

Table I — Measles Vaccine

Type	Date of Licensure	Strain	Manufacturer	Brand name
Inactivated	1963	—	Lilly Pfizer	Generic Pfizer Vax Measles K
Live attenuated	1963	Edmonston B	Lederle Lilly MSD Parke Davis Pfizer	M Vax Generic Rubeovax Generic Pfizer Vax
			Phillips-Roxane	Measles L Generic
Live further attenuated	1965	Schwartz	Dow Merioux	Lirugen Rouvax
	1968	Moraten Schwartz	MSD Smith-Kline RIT	Attenuvax Rimevax
Live further attenuated		(1) Edmonston-Zagreb (chick embryo fibroblast) (2) Edmonston-Zagreb-Ikic Human Diploid cell	Under trial	

Route of administration It may be subcutaneous, intradermal or intramuscular, Inhalation of Aerosolized vaccine has been successfully tried with the E-Z-CEF and the HDC vaccine.

Side Effects and Adverse Reactions

Mild side effects in the form of fever and rashes are fairly frequent. In a multicentric study, 14,994 vaccinees were studied. Side effects observed were fever (8.3%), diarrhoea (3%), respiratory catarrh (0.9%) and rash (0.7%) (24). The estimated rates for serious adverse reactions following measles and measles vaccination is shown in Table II (25).

Table II — Adverse reactions to Measles and Measles vaccine

Adverse reactions	Measles complications/ 100,000 cases	Measles vaccine adverse reactions/ 100,000 vaccines
Encephalitis/ Encephalopathy	50-400	0.1
SSPE	0.5-2.0	0.05-0.1
Pneumonia	3800-7300	—
Convulsions	500-1000	0.02-190
Death	10-10,000	0.02-0.3

Efficacy

A single injection of live vaccine produces antibody response in 85-95% in 9-15 months of age. The seroconversion rates in different age groups is shown in Table III. Seroconversion rates with the newer vaccines are listed in Table IV. (26-30)

Contraindications

Children with anaphylactoid reactions following egg ingestion and neomycin use should not receive the vaccine. It is also

Table III — Seroconversion with measles vaccine at different ages

Place	Reference	Age Group in months	Seroconversion (%)
USA	26-29	6-7	28.6
		8-9	56.5-88
		10-12	72.2-90
		12-15	93.8
Kenya, Cameroon, Haiti	3, 30, 31	6	45.1-52
		8	76.9-86
		9	84.5
		9-12	90
		13-24	96
India	18, 32, 33	6-8	66-86
		9-12	84-94
		12-15	85-98
		17-20	100
		21	100

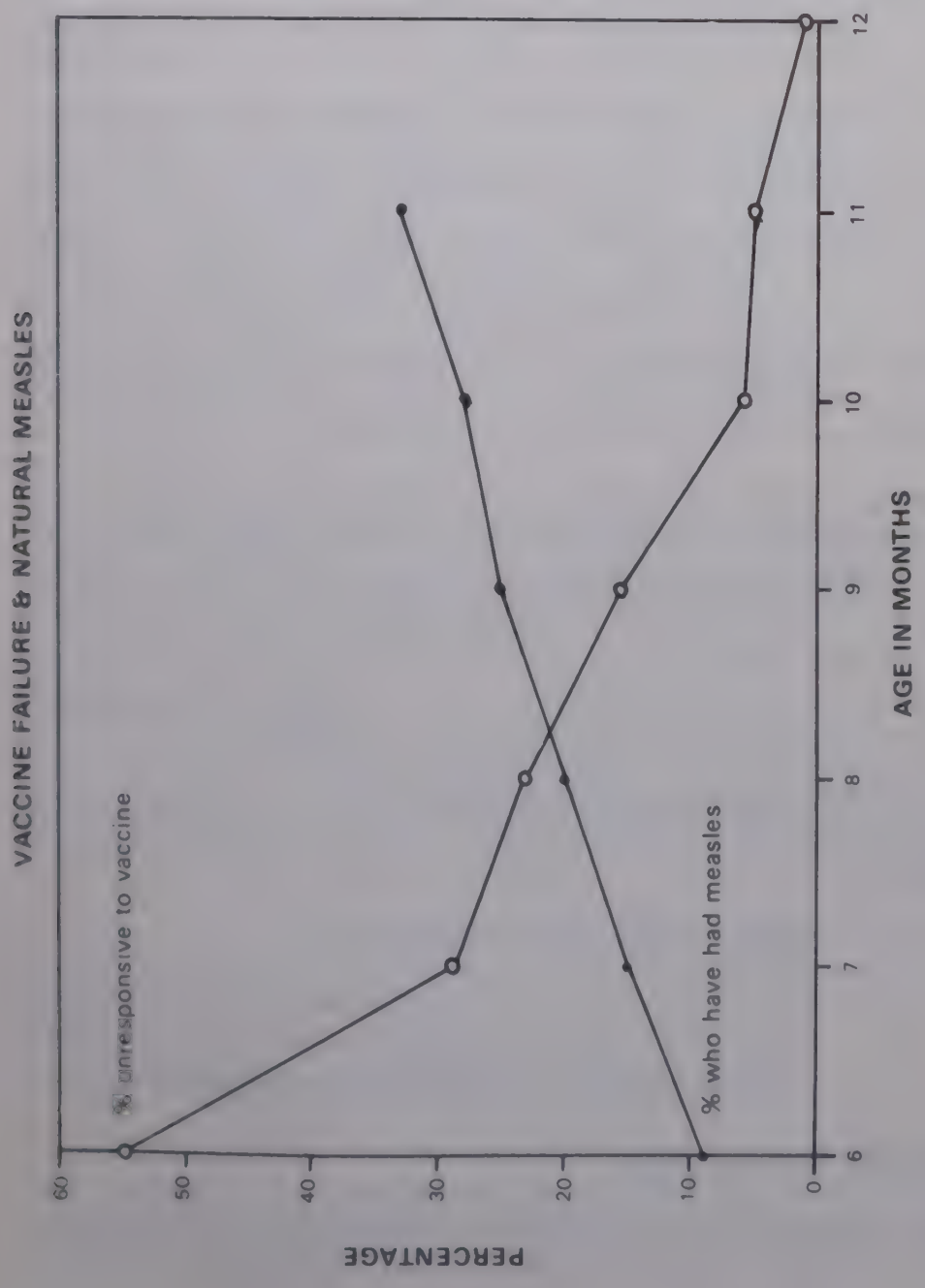
contraindicated in pregnancy, immune deficiency states, in persons receiving immuno-suppressive drugs and those with untreated tuberculosis. Respiratory, gastrointestinal and skin infections, malaria and protein energy malnutrition are not a contraindication to measles vaccine (25, 31, 34).

Age of Vaccination

Refractoriness to vaccine in the first year of life is principally mediated by measles specific IgG antibodies acquired transplacentally. On the other hand, in natural measles infection, the primary route of invasion is the respiratory tract. Since infants do not receive secretory IgA antibodies transplacentally, deposition of the virus on unprotected respiratory mucosal cells initiates a local infection that can overcome the protection offered by the persisting maternal IgG antibodies. Hence infants can develop natural measles infection despite having maternal antibodies in the blood. On the other hand, an innoculum of vaccine virus introduced subcutaneously is rapidly neutralised before suffi-

cient viral replication occurs to produce a critical mass of measles antigen capable of initiating host immune responses (2). The higher the level of maternal IgG, the lower is the seroconversion rate (23, 31, 35).

In the early sixties it was believed that maternal antibodies did not persist beyond 6 months. Later it was found that infants had antibodies upto 12 months (36, 37). However an Indian study revealed no maternal antibody beyond 8 months (38).



The optimum age for measles vaccination must take into account the local epidemiology of the disease. The rate of acquisition of natural measles by age must be compared with vaccine failure by age (Fig. 1). In India, the attack rate below 6 months is very low as only 1.7% cases of measles occur below that age (39) but seroconversion following vaccination between 6-8 months of age has been reported to vary between 66-86% (32, 33). These children would warrant another injection beyond one year of age to ensure complete protection. This will entail incorporation of two visits to the health services with extra expenses and inevitable drop outs upto the order of 74% (8). On the other hand, vaccination with a single dose at 9 months produces seroconversion in 85-95% and requires no further boosters (18, 32, 33). Similar reports are available from other developing countries (8, 9, 31). Therefore the WHO and the UIP of India recommend a single dose of Measles vaccine at 9 months (40, 41). This still leaves about 15% of children between 6-9 months of age who could develop measles. It is recommended that during epidemics or when there is a household contact, infants as young as 6 months may also be vaccinated. (*vide infra*)

In sharp contrast to the above, studies from developed countries show that the median age at which children suffer measles is 4-6 years (14). Lower seroconversion was noted when vaccination was performed less than 12 months (79-85.4%), as compared to 15 months (95%) of age. (20, 42-44). Seroconversion at 8-9 months was reported to be as low as 56.5%. This led to the recommendation of vaccination at 15 months in these countries.

Halsey and co-workers (31) proposed that the increased seroconversion in developing countries in lower age groups may be because :

1. Mothers have low HI antibodies
2. Infants may lose their passively acquired antibodies faster because of an increased catabolism of matemal antibodies due to protein energy malnutrition.

Need for Revaccination

Most observations (or recommendations) for the need of re-immunisation especially when primary immunisation was per-

formed at less than one year, were based on the longitudinal studies of HI antibody levels (26, 28, 44). A drop in HI antibody was equated with waning immunity. This concept of the equivalence of a drop in HI antibody to a waning immunity has not been subsequently substantiated (42, 45) making revaccination unnecessary for those who demonstrate seroconversion with the initial dose. For those who do seroconvert, immunity is life long. For those 5-15% children who do not seroconvert when vaccinated at 9 months, the cost of identifying and revaccination would be enormous and at least cannot be justified on a national scale (46).

A possible harmful effect of early vaccination followed by revaccination was put forward by Wilkins and Wherle (28) and Linneman (26). They observed that 40-57% of children vaccinated at less than one year of age did not develop HI antibodies following a second dose of vaccine, given beyond one year of age. They proposed that this was due to the development of neutralising antibodies which interfered with subsequent development of HI antibodies (26, 28). However this has not been upheld by subsequent workers (29).

The widespread use of vaccine may increase the age at which measles develops. If this occurs and high immunisation levels are maintained, then, age of immunization will automatically be shifted to a higher age group (33).

Delayed Immunisation

There is probably no upper age limit for measles immunisation. When immunisation is delayed, simultaneous administration of multiple vaccines viz, OPV, DPT and Measles or MMR can be given at the same time (47). However, if different live virus vaccines are not administered at the same time, then a period of at least 4 weeks should elapse before the next live vaccine is given.

Storage & Transport of Measles Vaccine

The currently available vaccine should be stored at a temperature less than 8°C and should be transported on dry ice at a temperature less than 10°C. It should be administered within an hour of reconstitution.

Protection of children in an epidemic situation

In epidemics, infants as young as 6 months should be vaccinated. These children should however be reimmunized after 15 months of age (48).

Prevention among household contacts

It can be achieved by the use of immune serum globulin in the dose of 0.25 ml/kg of a 16.5% solution (Maximum dose is 15 ml) given intramuscularly within 7 days of exposure. It should be given to all susceptible contacts. After 3 months these children should be given active immunisation with measles vaccine (20, 49). Protection to household contacts can also be provided by the administration of live measles vaccine, provided it can be given within 72 hours of exposure. This would not only prevent measles but also confer life long immunity (43).

HEAT STABLE VACCINES

Rimevax made by Smith Kline-RIT, from a Schwartz strain seed lot has been found to be heat stable for upto 14 days at 37°C and 21 days at 20-25°C (30, 50, 51, 52). Heat stable Attenuvax has also been found to maintain minimum required potency of 10^3 TCID per dose for 14 days at 37°C. Reconstituted Attenuvax can also be stored at 25°C for 48 hours and 37°C for 4 hours (51). Seroconversion with both these heat stable vaccines was found to be satisfactory. Stability at higher temperatures would permit transport at ambient temperatures, provided temperature and time limits are not exceeded. However these vaccines are not yet generally available in our country.

AEROSOLISED VACCINE

The Edmonsten-Zagreb strain of chick embryo fibroblast vaccine and the human Diploid cell vaccine has been used as aerosol in immunizing children against measles (21-23, 53). The basic principle being that administering the vaccine by the respiratory route would avoid neutralisation by maternal measles IgG antibody as the latter is not secreted into the epithelial surface of the infants lung. Thereby children as young as 4-6 months have been successfully immunised (21, 23).

Vlatkovic et al (54) successfully vaccinated 12-17 months old by administering the vaccine intranasally with a syringe into both nostrils of a crying infant at the beginning of a deep spontaneous inspiration and obtained a seroconversion rate of 90%.

Table IV — Seroconversion with newer vaccines

Author	Vaccine (route)	Age group in months	Seroconversion rate (%)
21-23	E-Z, CEF		
	(I/D)	20-25	84
	(S/C)	20-25	84
	(Aerosol)	4-6	37.5
		14-47	92.93
	(Intranasal)	12-17	90
21, 22	HDC-vaccine	4	69
	(S/C)	5	89
		6	100
	(Aerosol)	4-6 mo	87
		12-47	100

OVERVIEW OF THE CURRENT STATUS OF MEASLES IMMUNIZATION

As of December 1984, only 12% of children in the developing countries and 69% in the developed countries had been immunised against measles. The South East Asian region had one of the lowest coverages with a mere 5.0% having been immunised (Table V). USA has reduced its incidence of measles by nearly 99% by an intensive immunisation programme (45).

Measles vaccination in India was started as late as 1985-86. The yearwise proposed number of beneficiaries is shown in Table VI. The achievements of the year 1986-87 were only 67.5% of the target (55). As yet there appears to have been no impact of the UIP on measles, as a recent report from Rajasthan (56) showed

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that 3% of infant deaths were still being caused by measles even though Rajasthan's reported coverage of the year 86-87 targets was 236% (55).

Table V : Children immunized by 12 months of age (1985) – SEAR

Country	% immunized	Estimated eligible target ('000)
Bangladesh	1	3015
Bhutan	11	46
Burma	0	1323
DPR Korea	63	603
India	1	22170
Indonesia	15	4673
Maldives	32	7
Mongolia	18	65
Nepal	47	578
Sri Lanka	18	434
Thailand	28	1067

Table VI — The yearwise proposed number of beneficiaries.

Year	1985-86	1986-87	1987-88	1988-89	1989-90
No. in millions	2.3	5.7	10.0	14.2	18.3
%	10	25	45	65	85

The Ministry of Health & Family Welfare has targeted 85% infants to be immunised by 1990 but several workers are of the opinion that 90-95% need to be rendered immune to stop endemic transmission (57, 58).

STRATEGIES FOR IMPROVING IMMUNIZATION COVERAGE

Annual pulse immunisation has been carried out successfully every winter to drastically reduce the number of cases of measles. This strategy may be followed in areas with similar demographic characters, followed by concentric expansion of areas as more vaccinations become available (59, 60).

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Recommendations

1. Single dose of measles vaccine should be given at 9 months or at the earliest contact thereafter (upto 5 years). There is no need to revaccinate these children routinely.
2. In special situations (epidemics, house hold contacts) the measles vaccine may be given as early as 6 months of age. These children would however require a second dose at 15 to 18 months.
3. Heat stable vaccine should be made available for routine use.
4. Active immunization with measles vaccine should be offered to all susceptible house hold contacts of a measles case in order to decrease the severity of the disease in them.

Areas of Further Research

1. Studies need to be carried out to assess the efficacy of a single dose of measles vaccine given at 7-8 months of age.

Typhoid 5

Arvind Saili

EXTENT OF PROBLEM

Typhoid fever occurs in all parts of the world. A complete picture on the incidence of the disease is lacking since it is not a notifiable disease. Nevertheless the incidence is fairly high as is obvious from the available statistics. In 1980 an incidence of 0.47/1000 population was reported in India (1). In 1984 a total of 306, 258 cases were treated in medical institutions of India of which 627 died (2).. There does not seem to have been any decline in the incidence of typhoid in our country and it continues to be major public health problem.

Age Incidence of the reported cases, more than two third cases are in individuals less than 20 years of age and among them the highest incidence is seen in infants and young children (3) Patnaik and Kapoor (4) in a study showed that 18% of all cases occured in the 0-4 years are group. The case fatality rate in this age group was 2-3 times more than the older childern. Johnson and Adreic (5) in another study showed that 17% of all pediatric cases were in 0-4 years age group and the case fatality rate was higher. Kapoor & Man Mohan (6) showed an incidence of 52.2% in the age group 0-5 years among all pediatric cases. This compared well with the study of Mullighan et al (7) which showed an incidence of 60%, in this age group.

TYPES OF VACCINE

Monovalent vaccine Most of the countries including the U.S. are using this form of the vaccine since typhoid fever is mainly attributed to *S. typhi*. This is an agar grown, heat killed and phenol preserved vaccine containing 1,000 million of *S. typhi* per ml. It can also be prepared with acetone and the vaccine is then known as AKD (Acetone killed & dried) antityphoid vaccine.

Bivalent vaccine This contains *S. typhi* and *S. paratyphi* A in the proportion of 1000 million & 500 million organisms respectively. The organisms are killed and preserved by heating at 54°C for 1 hour and by addition of 0.5% phenol. This vaccine is prepared in

India by C.R.I., Kasauli which is also manufacturing a Pediatric vaccine containing 330 million bacilli of *S. typhi* and 165 million bacilli of *paratyphi A.* This vaccine can also be prepared by inactivation of the organisms with acetone in the dried form (AKD vaccine). CRI Kasauli has the capacity to manufacture AKD vaccine and makes it available on request.

TAB vaccine This is usually made up of a killed suspension of *S. typhi* 1,000 millions and *S. paratyphi A* and *S. paratyphi B* 500-750 million each per ml. WHO has recommended discontinuation of this vaccine because of low incidence of paratyphi B and a higher incidence of side effects of TAB vaccine.

NEWER VACCINES

Live oral vaccines Live attenuated strains of *Salmonella* are showing promise as live oral vaccines against human typhoid fever and other salmonella infections of man and animals. Attenuation can be achieved by introducing genetically defined, non reverting mutations into specific genes on the *Salmonella* chromosome. Mutations in the gal E or aro A genes of *Salmonella* inhibit the ability of the bacteria to grow *in vivo* and strains carrying such lesions are effective vaccines against salmonellosis (8, 9).

Ty 21a strain of *Salmonella* is a promising development on the typhoid immunization front. It consists of a mutant strain (Ty 21a) lacking in enzyme uridine diphosphate-glucose-4-galactose-epimerase, an enzyme necessary for the completion of the O side chain of the bacterial lipopolysaccharide cell wall. When swallowed, the organism undergoes 4 or 5 cell divisions, penetrates and infests the wall of small intestine and then self destructs. The vaccine is safe, stable and protective for a period of at least 3 years (9).

Vi Polysaccharide Parenteral vaccine The Vi polysaccharide of *S. typhi* covers the bacteria as a capsular antigen and has a known virulent property. In an attempt to purify Vi antigen under non denaturing conditions, *S. typhi* has been treated with hexadecyl trimethyl ammonium bromide. Two separate lots of Vi vaccine have been prepared by this method, one at NIH, USA and other at Merieux Institute in France. Both vaccines elicited significant rise in Vi antibody except that NIH preparation caused some

adverse reactions which was attributed to the residual LPS in the vaccine. The vaccine is being evaluated in controlled field trials in Nepal and South Africa. Preliminary results indicate 65% efficacy for at least 6 months (11).

Storage of Vaccine Phenolised typhoid vaccine is stored in dark at a temperature below 8°C but it should not be frozen. AKD vaccine, can be stored at room temperature for at least 3 years. The oral typhoid vaccine is stored at 4°C.

Dosage and Mode of Administration Committee of Infectious Diseases (USA) recommends primary immunization with acetone killed typhoid vaccine in children one to 10 years with a dose of 0.25 ml subcutaneously on 2 occasions separated 3 weeks apart. For individuals older than 10 years two doses of 0.5 ml each are given. Booster is recommended every 3 years in endemic areas (12). Typhoid vaccine is not recommended below 1 year of age.

Under Expended Programme of Immunization (EPI) in India, a dose of 0.5 ml on 2 occasions between 5 and 6 years of age was being given with booster every 5 years (3).

Vaccine is given subcutaneously. Intramuscular route causes more severe reactions.

Tuft (13) introduced intradermal method of immunization employing 0.1 ml of standard vaccine. No systemic reactions were seen and good titres were obtained.

ANTITYPHOID VACCINE TRIALS

Parenteral killed whole cell typhoid vaccines have been available since 1896. In the 1950 & 1960 the WHO sponsored a series of large scale field trials in several countries to assess the efficacy of various types of parenteral killed whole cell vaccines.

A controlled field trial of antityphoid vaccines was carried out in 25 regions in Poland (13). Four types of vaccines were used. A total of 690,655 persons received 2 inoculations at intervals of 7-10 days. This was followed by 2 years surveillance period. It was concluded that the formol killed phenol preserved vaccine was the most effective and Grasset's vaccine the least.

WHO sponsored field trials (14, 15) found that the acetone inactivated vaccine (K) was superior to the phenol invactivated (L). This is attributed to the fact that treatment with acetone resulted in the adhesion of the Vi antigen to the bacterial cell whereas this did not occur with the heat killed phenolized vaccine. It was also suggested that the higher potency of the acetone vaccine was due to the removal of a toxic factor by extraction with acetone. Trials in Yugoslavia (16) and Guyana (17) showed that the acetone dried and heat phenol inactivated dried vaccine were both superior to the heat phenol inactivated liquid vaccine but out of the acetone killed vaccine and heat killed phenolized vaccine the former was superior. The acetone dried vaccine afforded a protection of 79-93% whereas the heat phenol inactivated vaccine afforded a protection of 47-77% (18) Surprisingly the Acetone vaccine is still largely unavailable and most manufacturers make the phenolized vaccine.

Major thrust now is on live oral typhoid vaccine. Two attenuated *S. typhi* strains used as live oral vaccine (Ty 21 a and 541 Ty) have shown promise with decreased incidence of adverse reactions Wahdan et al (20) evaluated the efficacy of this vaccine in a trial in Egypt. Three doses of the vaccine were given to children within a week after prior ingestion of sodium bicarbonate tablets. The vaccine was given as a liquid suspension. No adverse reactions were encountered. During the 36 months period of surveillance the vaccine provided 96% efficacy. Extensive field trials have also been carried out in Santiago, Chile (21) Various formulations and immunization schedules were evaluated. It was observed that the enteric coated capsules were significantly more protective than vaccine in the gelatin capsule or with sodium bicarbonate formulation. It was also observed that 3 doses of enteric coated Ty 21a given within one week provided 67% protection for at least 3 years. This was comparable with the protection afforded by the heat phenol inactivated parenteral vaccine but the notable difference was the absence of any adverse reactions with the enteric coated Ty 21a. Oral vaccine also apparently created a herd immunity effect due to which, the incidence increasingly dropped in the control group areas also.

TYPHOID VACCINE IN EPI INDIA

The Government of India after a meeting held in January 1988

recommended the discontinuation of Typhoid vaccine in EPI for school children (22). The reasons forwarded for this recommendation were :

a) Information on the epidemiology of enteric fevers in different parts of the country is inadequate and even the size of problem is not adequately known.

b) In a limited study in the urban slums of Delhi, it was found that less than 1% of the children get disease each year.

c) The conventional type vaccine used was affording a protection range of 51-73% while acetone killed vaccine gave protection from 79-94% for a period upto 3 years. In India the conventional type vaccine was being used.

d) The vaccine is associated with local and constitutional side reactions and therefore there is general resistance on the part of children to accept it and as a result the performance in EPI has been consistantly low.

e) Acetone killed vaccine trials may be conducted by ICMR in India and depending on the outcome its use in public health practice could be reviewed.

However the available statistics points to a fairly high incidence of the disease in India (1–6). A spurt in positive blood cultures for *Salmonella typhi* has been seen at Salmonella reference centre at Lady Hardinge Medical College, New Delhi (151 positive cases in 7 months of 1988 compared to 64 cases in whole of 1987). Even if 1% of the urban slum population gets the disease in a year, as brought out by the Committee itself, it points to a very high incidence. Further as we have already seen there has not been any decline in the incidence of enteric fever in the country. It would be prudent therefore that typhoid vaccine should continue in the EPI programme.

AKD vaccine has been proven to have greater efficacy as accepted by the Committee itself and it does not require any further trials. It should be made available for general use as facilities for manufacturing this vaccine already exists in the country. Currently available phenolised inactivated vaccine should be gradually replaced by AKD vaccine.

As the incidence of typhoid is fairly high among under five children (4-6) it is imperative that the vaccine be commenced at 2 years of age. If AKD vaccine is used, a booster will be required every 3 years.

Extensive field trials with oral live typhoid vaccine (Ty 21a) should be carried out in our country.

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Recommendations

1. Typhoid vaccination must continue as a part of National Immunization Programme.
2. Two primary doses at 4-6 weeks interval should be given between 2-3 years of age or at the earliest contact thereafter.
3. Single booster dose should be given every 3 years.
4. Monovalent vaccine containing only Salmonella typhi should be made available.
5. Acetone killed freeze dried vaccine should now be manufactured in the country as against currently available phenol killed vaccine However phenolised vaccine should be used till that time.
6. Intradermal route should be preferred over subcutaneous route. However in absence of trained personnel, subcutaneous route may be used.

Areas of Further Research

1. Multicentric field trials with live oral typhoid vaccine (Ty 21a) should be conducted before its routine use can be recommended.

Cholera 6

Vinod K Prasad & Harish Kumar

INTRODUCTION

Cholera also known as asiatic cholera to the western world, has been ravaging the mankind for times immemorial. Known to Indians as *Vishuchika*, its outbreaks have wiped large areas of human population time and again.

MAGNITUDE OF PROBLEM

The seventh pandemic which had started in 1961 from Sulawesi islands in Indonesia and reached India in 1964 has travelled far and wide involving almost all parts of the world (1). Global experience in last 25 years has shown that cholera can be introduced in any country but can create a problem only in areas where other acute enteric infections are endemic and where sanitation is defective (1, 2). These cases all over the world were almost exclusively caused by El Tor Vibrio of Ogawa and Inaba strains with the former predominating (1).

The menace of cholera remains unabated in our country as evidenced by large scale outbreaks from time to time.

VACCINES AGAINST CHOLERA

Soon after the discovery of cholera bacillus by Robert Koch in 1884, immunization against cholera was attempted. Two efforts in 1884 and 1888 were followed by Haffkine's study in 1892 (3). Numerous oral and parenteral, killed and live vaccines have since been under trial and use (Table I).

Table I — Types of Killed Cholera Vaccine for Parenteral use

Whole Cell Vaccine	Chemical Vaccine
1. Phenol inactivated, phenol preserved. (Currently in use).	1. Purified LPS*(Ogawa)
2. Heat inactivated phenol preserved.	2. Purified protein-LPS* (Inaba)

Whole Cell Vaccine	Chemical Vaccine
3. Formalin inactivated	
4. Organic mercurial inactivated and preserved.	

LPS* — Lipopolysaccharide

Vaccine employed at present in India is a saline suspension of approximately 6,000 million each of classical Ogawa and Inaba serotypes of V. cholera 01, per ml. It is available in single or multidose ampoules to be stored between 0-20°C. It is turbid and should be shaken well before use. Primary immunization consists of two doses injected subcutaneously or intramuscularly at an interval of 4-6 weeks (1, 2). Dose depends on the age (Table II).

Table II—Recommended dose of cholera vaccine for primary immunization

	Ist dose	*2nd dose*
Adult & children over 10 years	0.5 ml	0.5 ml
2-10 years	0.3 ml	0.3 ml
1-2 years	0.2 ml	0.2 ml

Vaccine is not given to children under 1 year of age (1). If for any reason, immunization cannot be carried out in 2 doses, a single dose equivalent to double of the first dose should be given. Boosters are recommended every 6 months (1).

Vaccine Efficacy

From 1963 to 1977, 12 well controlled field trials have been carried out in Bangladesh, India, Phillipines and Indonesia. The purpose of this review is to give some perspective to our present ability or perhaps more correctly, inability to immunize adequately against this disease.

Degree & Duration of Protection

Period of protection is short. Generally it does not exceed 3-6 months, declining rapidly after 3 months. Long duration of protection was offered only in early Bangladesh trials (4, 5). Similar degree of protection was not seen in subsequent trials (6, 7). The efficacy of cholera vaccine according to various trials has been 50-60% only (6-10).

From many studies done so far, it is clear that long term protection (i.e. over several cholera seasons) is not to be expected with the usual run-of the mill vaccine. On the other hand, recent reports from Indonesia (6, 7) have shown that the duration of protection with cholera vaccine can be significantly extended by the use of aluminium adjuvant vaccine. These studies also demonstrated good protection to children under 4 years of age as against the conventional vaccine.

Effectiveness of cell Free Vaccines

Purified cell free LPS Ogawa antigen and protein -LPS Inaba may afford similar degree of protection as whole-cell vaccines (2, 4, 5).

Effect on Severity

Vaccination has no effect on the severity of clinical cholera (2).

Cross Protection Between Serotype and Biotype

Vaccines produced with *V. cholera* classical biotype strains protect against disease caused by biotype El Tor (9-12). The reverse protection was also seen in the first Phillipines trial (11). Inaba vaccines offer a high degree of cross protection against Ogawa infection but Ogawa vaccine protects poorly or not at all against Inaba infection (13).

Role of Vaccines in Cholera Prevention and in Control of Epidemics

In the past, vaccination has been greatly overrated as a preventive measure for cholera. But in recent years it has been shown that the presently available cholera vaccination do not prevent inapparent infection, nor do they prevent introduction of cholera

in a particular community (1, 2, 13, 14). In both Bangladesh (4) and Phillipines (10), no significant difference in culture positivity was found in family contacts who had or had not received vaccination.

Further more, vaccination did not affect the percentage of symptomatic individuals requiring treatment and did not alter the severity of hospitalized cases (15). It does not prevent development of carrier stage nor does it limit the spread of infection and thus it has no role in controlling the epidemics (1, 2, 14). The vaccination programme usually does not adequately reach the most susceptible segment of the population. On the other hand anti-cholera immunization creates a false sense of security to both recipients and health administrators (1).

Mass vaccination as is usually practiced at the commencement of an epidemic, is considered a waste of time and valuable resources. Moreover, serum hepatitis, a serious problem has been found to follow mass vaccination campaign in a number of countries (16).

It would be pertinent to mention that attainment of high standards of sanitation and personal hygiene would not only make a country free from cholera but will also make it non-receptive to cholera infection and thus bring about a permanent solution to the problem (16).

International Cholera Certification

The WHO in May 1973 abolished the requirement of a cholera vaccination certificate for International travel, although a few countries (e.g. Sudan, Libya) continue to demand such a certificate. The international vaccination certificate is considered valid for a period of 6 months starting from sixth day of injection. Single dose is sufficient to satisfy international health regulation. A revaccination before the expiry of 6 months renders the certificate valid for another 6 months (17).

Oral Vaccines

As presently available vaccine does not give adequate protection, the need for better vaccine has long been felt. The search has focussed on oral immunization because of enteric route of infection of the natural disease.

Non Living Oral Cholera Vaccines

A large scale controlled field trial was done in Maltab area of Bangladesh to assess the effectiveness of killed whole cell (WC) oral vaccine with or without B subunit (BS). Vaccines were produced by Merieux Institute, Lyon France. 63,498 children between 2-15 years and women more than 15 years were studied. Surveillance upto 6 months after 3rd dose indicated 26 cases of confirmed cholera in the placebo group and 4 cases in the BS WC group (protective efficacy 85%) and 11 cases in WC group (protective efficacy 58%). BS-WC vaccine had 92% efficacy in 2-10 years age group and 77% in more than 10 years age group as compared to 53% and 62% with WC in the two age groups respectively (18). Follow up of the same field trial shows that after 2 years the protective efficacy of BS-WC was 26% and that of WC was 22% (19). They also noticed that incidentally this BS-WC vaccine also cross-protected against diarrhoea due to enterotoxigenic strains of Esch. coli that produced heat labile toxin similar to cholera. Subsequently a higher dosage of same vaccine was given on 3 occasions to healthy young adult North American volunteers with sodium bicarbonate and cimetidine. It gave moderate protection (64%) after an experimental challenge (20).

Another new killed oral vaccine has been produced by Pasteur Institute by the crude fraction of the V. cholera 01 cell wall. Results of preliminary tests in Zaire have shown it to be protective when given in 2 doses, 8 days apart (21).

Live Oral Attenuated Vaccines

First fully evaluated product of Honda and Finkelstein (22) was the "Texas Star-SR" strain. This strain was obtained by chemical mutagenesis and lacked a subunit activity (which is responsible for diarrhea) but retained B subunit synthesis (which is immunogenic). This strain was tested in 68 healthy volunteers in USA. It stimulated anti cholera antibodies in 93% of the vaccinees. Although free from other side effects it caused mild diarrhea in 24% volunteers (23).

CONCLUSIONS

Presently available parenteral cholera vaccine with poor efficacy and short duration of protection can not be recommended for inclusion in any immunization programme.

It s role in epidemics is not justified. More emphasis should be laid on other measures like sanitation and water supply. ORS may be more effective in controlling mortality.

Further research should be carried out for developing more effective oral cholera vaccine.

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Recommendations

1. Available cholera vaccine is not recommended for routine use in endemic area.
2. It is *useless* in combating an epidemic and only provides a false sense of security. Cholera epidemics are best prevented by ensuring safe drinking water and proper sewage disposal and best managed by creating neighbourhood treatment facilities with abundant ORS supply.

Viral Hepatitis 7

Madhulika & Harish Kumar

Acute viral hepatitis is a systemic infection affecting the liver predominantly. Four types of viral agents have been implicated. Hepatitis A (HAV), Hepatitis B (HBV), Non A non B (NANB) agent and the recently described HBV associated delta agent. All four types produce clinically similar illnesses. These range from asymptomatic and inapparent to fulminant and fatal acute infection on one hand and from sub-clinical persistant infection to rapidly progressive chronic liver disease with cirrhosis and even hepatocellular carcinoma on the other (1).

SEROLOGICAL MARKERS OF HEPATITIS

Serological markers of HAV, HBV and delta infection are available (2). Different markers are detectable at different stages of diseases (Table I). No markers are available for Non A Non B and this remains a diagnosis of exclusion.

Table I — Serologic Markers of Hepatitis (2)

A. HEPATITIS A (HAV)		
Serological Marker	Definition	Significance
Anti-HAV	Total antibody (IgM and IgG subclasses) directed against HAV	Indicates recent acute (IgM) or past HAV infection (IgG) Confirms past exposure and immunity towards HAV
Anti-HAV-IgM	IgM antibody in HAV	indicates recent acute infection

B. HEPATITIS B (HBV)

BHsAg	Hepatitis B surface antigen — found on the surface of the intact virus and in serum as unattached particles (spherical or tubular)	Indicates infection with HBV (either acute or chronic)
HBcAg	Hepatitis B core antigen — found within the core of the intact virus	Not detectable in serum (found only in liver tissue)
HBeAg	Hepatitis B core antigen — (soluble antigen produced during self cleavage of HBcAg)	Indicates active HBV infection. Signifies high infectivity. Persistence for 6-8 weeks suggests chronic carrier and/or chronic liver disease.
Anti-HBs	Antibody to HBV surface antigen (HBeAg) ; subclasses IgM (early) and IgG	Indicates clinical recovery from HBV infection and immunity, protective
Anti-HBc	Total antibody to HBV core antigen (HBcAg)	Indicates active HBV infection (acute and chronic)
Anti-HBc-IgM	IgM antibody to HBcAg	Early index of acute HBV infection Rises during acute phase then declines. Not present in chronic HBV
Anti-HBe	Antibody to HBe Antigen (HBeAg)	Seroconversion (HBeAg to Anti HBe) indicates resolution.

C. DELTA AGENT (HDV)		
Anti-HDV	Total antibody to the Hepatitis D (Delta) Virus	Indicates exposure to the agent (HDV) Patient may transmit HDV infection.
HDV RNA	RNA of the Hepatitis D (Delta) Virus	Present in serum

INCIDENCE

Incidences of different hepatitis agents vary according to the type of clinical illness and is different in children and adults (3) and is shown in table II.

Table II — Incidence of various types of Hepatitis agents in India (3)

	Sporadic hepatitis		Fulminant Hepatitis	Subacute Hepatitis
	Adults %	Children %	%	%
HAV	14	67	12	6
HBV	42	9	36	48
NANB	44	24	52	46

MODE OF INFECTION

HAV spreads by orofecal route while HBV largely spreads by prenteral route i.e. by contaminated needles, blood transfusions etc. NANB spreads both by parenteral route (1) and also by orofecal route (3). In India and other Asian countries it is believed to be the major cause of hepatitis epidemics (3).

Vertical transmission of HBV from mother to the infant can occur (1, 2, 4), HBsAg is present in almost 4% of pregnant mothers and is a poor indicator of vertical transmission. On the other hand 70-90% of infants born to mothers with detectable HBeAg in the serum develop hepatitis with in 6 months (2, 4, 5,). Only 10 to 20% mothers with anti HBe antibody transmit this infection (4-6). Infection in the neonate can be diagnosed by detecting HBeAg or Anti HBc IgM antibodies in the blood of the infants at around 3-4 months of age (7). The infection in infants is mostly asymptomatic but chronic active hepatitis may develop (7).

PREVENTION

General Measures

Environmental sanitation with safe water supply and sewage disposal and personal hygienic measures designed to curb the orofecal route of spread remain the main stay of prevention of HAV and for NANB infection in our country. For HBV and delta agent and some cases of NANB infection hygenic measures designed to curb the parenteral route of spread like screening of blood donors, disposal of contaminated needles (8) etc. remains the mainstay of prevention.

Passive Immunization

Immune serum globulin (Standard gamma globulin 16.5%) in doses of 0.02 ml/kg given as soon as possible after exposure has an efficacy of over 95% in preventing HAV infection (9) Short term visitors from abroad should be given this injection on arrival in India. Its effect lasts for 5-6 weeks and if required it can be repeated after that time. In western countries it is also recommend for all household contacts of HAV cases (8, 9) but considering that India is an endemic country wherein the exposure is continuous and not necessarily from household contacts only, the same cannot be recommended in our country. Role of immunoglobulin in preventing parenteral NANB infection is not established and at present it cannot be recommended (8).

Similarly it has no role in prevention of HBV or delta infection. Its role in the prevention of epidemic NANB is still controversial.

For passive immunization against HBV infection, presently hyperimmune Hepatitis B globulin (HBIG) is available. it is indicated in following situtions (8) :

a) Accidental needle exposure
b) Mucocutaneous exposure to blood
c) Babies born to HBsAg positive mothers.

Recommended dose is 0.06 ml/kg to be given as soon as possible after exposure and repeated after 1 month if the contact is confirmed to be HBsAg positive. For newborns, with suspected perinatal transmission a dose of 0.5 ml. should be given with in 12 hours of birth (and not later than 48 hours) followed by two doses at 3 months & 6 months. Passive immunization with HBIG is not effective against post transfusion hepatitis (8).

Active Immunization

There is no active immunization agent available for HAV, NANB or delta infection.

Hepatitis B Vaccine Two vaccines are in use viz. Plasma derived vaccine (10,11) and a recombinant DNA vaccine (12, 13). Both are equally effective and safe. At present only plasma derived vaccine (alum adsorbed) is available in our country. This vaccine is derived from plasma of asymptomatic human carriers of HBV. It is inactivated by treatment with formalin, 8 m urea and pepsin at pH2 successively. It has an efficacy of 85-95% and immunoity may last for as long as 5 years. Seroconversion in immunocompromised hosts may be as low as 25%. If infants are vaccinated between 6-12 months of age, decline of antibodies may occur by 6 year of age. HBV vaccine is indicated both before and after exposure to HBV infection (2,11).

Preexposure prophylaxis Pre-exposure propylaxis is recommended for certain high risk groups :

a) Medical personnels

b) Patients on hemodialysis, or those requiring repeated blood transfusions (thalassemia) or blood products (hemophillia).

c) Illicit drug users.

d) Household members and sexual contacts of HBV carriers.

e) Immunodeficiency syndromes, malignancies.

f) People visiting endemic areas like India may be considered for HB vaccine.

For pre-exposure prophylaxis 3 injections are required as for post exposure prophylaxis *(vide infra)*

Post exposure prophylaxis

Perinatal — Apart from HBIG (*vide supra*), HB vaccine in a dose of 0.5 ml should be given I.M. within 7 days with two further doses at 1 month and 6 months of age. It can be given on the same day as DPT.

Percutaneous/Mucosal exposure — HBIG in a dose of 0.6 ml/kg I.M. is given within 24 hours and then active immunization with HB vaccine is started within 7 days. The dose is 0.5 ml (10 ug) for children below 10 years and 1.0 ml (20 ug) above that age. Two more doses are required after 1 & 6 months respectively. Injection is given I.M. in deltoid region as immunogenicity following gluteal injection is poor (8). Dose is doubled for immunocompromised individuals. In healthy immunocompetent hosts, no boosters are required. There is hardly any contra-indications and it can be given even during pregnancy.

Recombinant DNA Vaccine (12, 13). It is produced by common Baker's Yeast into which a plasmid containing the gene for HBS Ag protein 0.5 mg/ml adsorbed with aluminium hydroxide. Thiomersal is used as preservative. It produces protective antibodies in over 95%. In children less than 12 years, 99% develop protective antibodies. On the other hand only 67% of

hemodialysis or immunocompromised patients develop protective antibodies.

It should be stored at 2°C-6°C and should not be frozen. Dose recommended in 5 ug for children less than 10 years of age and 10 ugm for older individuals. 3 doses at 0, 1 & 6 months should be given intramuscularly. For patients on hemodialysis or having immunodeficiency states, dose is increased to 40 ugm.

There is no risk of transmitting infection with this vaccine.

CONCLUSIONS

General measures of prevention are more important in preventing hepatitis especially the more prevalent HAV & NANB.

Passive immunization with Immunoglobulin against HAV although effective can be recommended only for international travellers to endemic areas.

Facilities for detecting HBV infection and for preventing it with HBIG and HB vaccine should be more widely available. High risk groups should definitely be given HB vaccine.

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Recommendations

1. There is a great need to establish properly equipped laboratories to study the epidemiology of viral hepatitis in the country.
2. Routine use of Gamma globulin among household contacts of HAV cannot be recommended at present because of high endemicity of the disease in the country.
3. Hepatitis B vaccine should be available for high risk cases and for newborns with proven perinatal transmission.

Areas of Further Research

1. Detailed epidemiological studies of viral hepatitis with various hepatitis markers.
2. Family studies for assessing the incidence among household contacts in our country.

Rabies 8

Harish Kumar and Vinod K Prasad

Rabies is one of the most terrifying, dreadly and oldest disease of man. In our country, it accounts for approximately 25,000 deaths every year. More than 5 lakh persons undergo anti-rabies immunisation annually (1). The man gets the disease from the animal of which the principle reservoir in India is dog. There has been a distinct increase in mortality and morbidity due to rabies over the past few years. This is attributed to two factors (1).

1. Increase in dog population which has now touched the figure of 80 million.
2. Absence of any effective Rabies Control Programme in the country.

Two epidemiological cycles of rabies are distinguished i.e. Urban & wild (sylvatic) (2). 99% of human cases in India are due to bites by urban rabid animals which maintain a cycle amongst themselves. Only 15-30% of human beings severely bitten by proven rabid animals develop rabies (3). Frequency of rabies depend on the site of exposure. Incubation period varies from 9 days to one year with an average of 2 months (4) but in rare cases may exceed 2 years. Children, particularly boys, because of their inherent fondness for dogs tend to bear the brunt of the disease (1, 2).

RABIES IMMUNIZING PRODUCTS

Both active (vaccines) and passive (rabies immunoglbulin) agents are available for protection against rabies (5,6).

Active Immunizing Agents These are of three types (6):

Nerve tissue vaccine Those derived from nerve tissues of adult animal, (e.g. sheep, goat, rabbit) or new-born animals (e.g. rabbit, rat, mice).

Duck Embryo Vaccine Derived from avian tissues (e.g. Duck embryo)

Tissue culture vaccines Vaccines prepared in cell-culture e.g. Human diploid cell (HDC) and purified chick embryo cell (PCEC) vaccine.

NEVER TISSUE VACCINE

At present it is the most widely used vaccine in India. This is because of the simplicity of its manufacturing procedure and very low cost (7). Sample type vaccine is most commonly employed and contains virus inactivated with beta-propiolactone. The vaccine contains 5% weight by volume (W/V) rabies virus infected sheep brain. The dose depends on the age and on the class of exposure (Table I). This vaccine is no more used in developed countries of the world because of severe side effects associated with its use. Apart from local reactions like pain, redness etc, it can also cause allergic reactions. Its most dreaded side effect is neuroparalytic reaction which may occur in 1 : 2000 to 1 : 8000 vaccinees (4).

Three types of neuroparalytic complications are clinically recognisable (8) :

a. Lumbo-dorsal type (Mortality 5%).

b. Landry type (Mortality 20-40%).

c. Neuritic type.

In view of the side effects, there is an urgent need to reevaluate its continued use in the national health programme especially when much safer vaccines are now available in the country itself.

DUCK EMBRYO VACCINE

It is not available in India and has lost its importance over the years because of its low antigenicity (9,10)

HUMAN DIPLOID CELL VACCINE (HDCV)

It is an inactivated virus vaccine produced from fixed rabis virus grown in W-I-38 or MRC-5 cell culture lines (5). It is used both for pre-exposure prophylaxis and post exposure protection It gives rise to high titre of the neutralising antibody in a short period and hence carries good immunogenicity (11).

For pre-exposure prophylaxis 3 doses of 1 ml, are given intramuscularly on, 0, 7 and 28 days. This results in development of protective antibodies in about 100% individuals (4). Smaller doses (0.1ml) given intradermally are equally effective for pre exposure prophylaxis (4). For post exposure prophylaxis 5-6 doses are given intramuscularly or subcutaneously on day 0, 3, 7, 14, 30 and 90.

Side effects of HDCV are seen very rarely and occur mainly in the form of local pain, erythema, itching, headache, nausea and abdominal pain. It is virtually free from neurological complications (5). Recently this vaccine has been successfully used by intradermal route for post exposure prophylaxis also (12, 13, 14). Different regimens of dosage have been tried but the one which employs 8 sites intradermal injection of 0.1 ml each, on day 0,4, and 7 and one booster each on D_{28} and D_{90}, has given the best results so far (14). This reduces the cost to 30% and decreases the number of visits leading to more compliance. But considerable skill is needed to give intradermal injection for restless young children. The small doses(0.1 ml each) usually recommended for intradermal route are *not* effective if given subcutaneously. Intradermal route has not been given approval by US. food and drug administration with the currently available 1.0 ml vials of HDCV as multi dose container for intradermal use (12), although the vial can be used for 7 days after reconstitution if kept at 4°C. (15). Simultaneous administration of chloroquine may also inhibit the immune response following HDCV (4).

PURIFIED CHICK EMBRYO CELL RABIES VACCINE

It is an inactivated tissue culture rabies vaccine propagated in primary chick fibroblast cell. The virus strain is Flury LEP adapted to grow in chick fibroblasts. The virus is inactivated by betapropiolactone and purified by zonal centrifugation. The production of the PEC rabies vaccine on primary chick fibroblasts allows a very high virus yield (16). This vaccine costs approximately one third that of HDVC but is equally effective when given after an exposure. Administration of PCEC by a multiple site

intradermal schedule of immunization, as tried for HDCV, could produce further savings, bringing the cost of post exposure treatment down to the level of nerve tissue vaccine. Moreover the cost savings of the intradermal route should further encourage pre-exposure immunizations in areas endemic for rabies (17). Studies for intradermal route of P.C.E.C. have still not been carried out but would definitely deserve a trial.

Side effects include local pain, erythema and swelling in less than 5% of the patients. Isolated instances of lymphadenopathy, headache, lethargy, slight elevation of temperature and allergic reactions of the skin have been reported. This vaccine has been used successfully in several countries including India (18).

Table I — Rabies Prophylaxis

NATURE OF EXPOSURE	STATE OF BITING ANIMAL		TREATMENT
	At exposure	During 10 days' follow up	
A. Skin licks, scratches	Available for observation grazes, minor bites on covered parts of arms trunk and legs.	Remains healthy	a) Initiate the course of vaccination with TCV-0, 3, 7 days and stop, if TCV not available N.T.V 3 ml OD × *5 days and stop.*
		Becomes rabid	b) Proceed to complete the course i.e. TCV on 14, 28 an 90 days or NTV for another 9 days (full 14 days)
	Not available for observation or Rabid		c) Besides completing the full course, these patients require administration of antisera on the day they are seen first ; half of the dose is infiltrated around the wound and the other half given intramuscularly.

NATURE OF EXPOSURE	STATE OF BITING ANIMAL		TREATMENT
B. Licking of mucous membranes, major bites (multiple or on face, head, fingers, neck etc).	Available for observation	Remains healthy	d) Treatment is as in (a) except that antisera (RIG) to be administered immediately as described in (c)
	Not available for observation or Rabid.	Becomes rabid	e) Continue as in (b) above f) Same as (c) above & RIG

TCV – Tissue Culture Vaccine (HDC or PCEC).
NTV – Nerve Tissue Vaccine.

USE OF SERUM AND RABIES IMMUNOGLOBULIN (RIG)

A horse anti-rabies serum made by the Central Research Institute, Kasauli, is available and is of proven additional efficacy in prevention of rabies if used soon after exposure. This serum is recommended for class 2 and 3 exposures and should be used in all bites of head, neck, hands and genitalia, at a dose of 40 IU/Kg as soon as possible after the exposure. Sensitivity testing must be done before administration to avoid serious reactions. Half the dose is infilterated around the wound and half is given intramusculary.

A human antirabies immunoglobulin (RIG) is available from a number of sources. Because it is of human origin, this immunoglobulin is much safer than horse serum and more expensive. The recommended dose of human RIG is 20 IU per kg (9).

CARE OF THE WOUND

All bites with suspected rabid animal should be thoroughly washed with soap and water immediately. Tetanus toxoid

should be given, if tetanus booster has been received within the last five years. Antirabies serum or RIG should be given immediately as described above.

CONTROL OF RABIES

This is best achieved by eliminating contact between the virus and humans. In practice this means that the disease must be controlled in dogs. Following strategies are recommended to control the menace of this disease :

A. **Control of Dogs :**

1) Owned dogs – vaccinated
2) Community dogs – vaccinated/removed
3) Stray dogs – removed.

B. **Health education** of masses along with the use of legislative measure should be properly enforced for immunization of dogs.

C. **Vaccination** Pre-exposure vaccination is recommended for veterinarians, animal handlers, lab workers and all those whose vocational or avocational pursuits bring them in contact with rabies.

Although developed countries use HDCV, for both pre and post exposure prophylaxis, PCECV appears to be the vaccine of choice for India because of its lower cost. More trials are recommended with this vaccine using both intradermal and subcutaneous route.

D **Sylvatic Rabies Control** — The last but not the least important measure is to control the sylvatic rabies with the help of veterinarians, epidemiologists and ecologists.

Thus rabies which has been controlled in Western countries can also be controlled in India, if continuous efforts by health authorities, administrators and above all public are put into practice in right earnest (19). Launching of a comprehensive National Rabies Control Programme is urgently required.

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Recommendations

1. It is essential that a National Rabies Control Programme be launched in the country at the earliest.
2. For post exposure prophylaxis it is important that tissue culture vaccines (like PCEC or HDCV) be available in the government hospitals & dispensaries. Dose schedule as recommended by NICD, be followed.
3. Facilities for procuring & manufacturing tissue culture vaccines should be set up in the country at the earliest so as to reduce the cost of these vaccines.

Areas of Further Research

1. Intra-dermal route of administration of tissue culture vaccine (particularly PCEC) should be studied to decrease the cost of total treatment.

Japanese Encephalitis 9

Harish Kumar & Madhulika

Japanese Encephalitis (JE) is a serious arboviral infection seen throughout most of the Far East and South East Asia. This entity has been noted in India since mid fifties. The first isolation of JE virus was made in Vellore from a human patient in 1958. Prior to 1970 Japanese Encephalitis was confined to South India, mainly the States of Andhra Pradesh and Karnataka. Subsequently however outbreaks have been reported from Assam, Bihar (Dhanbad), Delhi, Goa, Manipur, Orissa, Tamil Nadu, Tripura, Uttar Pradesh (Gorakhpur and surrounding districts, Lucknow) and West Bengal (Bankura) (1-6). Only states/UTS which have not reported JE cases during the last 10 years are Gujrat, Punjab, Himachal Pradesh, Rajasthan, Jammu & Kashmir, Sikkim, Dadra and Nagar Haveli, Daman & Diu and Lakshadweep (7). The number of cases, deaths and case fatality rates (CFR) in India since 1978 have been depicted in Table I (7).

Table I — Japanese Encephalitis cases in India (7)

Year	No. of affected states/ UTs	Cases	Deaths	CFR %
1978	18	7463	2755	36.91
1979	8	2845	926	32.54
1980	11	3478	1436	41.29
1981	10	3894	1167	29.97
1982	12	3516	1261	35.86
1983	9	1716	581	33.86
1984	9	3370	1405	41.69
1985	10	2490	916	36.78
1986	10	6500	2627	35.02
1987	10	2877	1172	40.74
Total	23	38149	14246	37.39

EPIDEMIOLOGY

JE is predominantly a rural disease, affecting mainly the lower soico-economic groups. Males are more frequently affected than females (ratio about 2 :1) (8). Children constitute 24.6 to 94% of reported cases in different outbreaks in India (7).

The disease incidence appears to be subsiding in China, Japan and the Republic of Korea, but at the same time has been increasing in parts of Bangladesh, Burma, India, Nepal, Thiland, and Vietnam. Epidemiologically, the outbreak of Japanese Encephalitis has been linked with the breeding season of mosquitoes.

PATHOGENESIS

JE is caused by an RNA virus of arbovirus group. 11 species of mosquitoes belonging to 3 genera have been incriminated so far as the vector of JE in India. More than eleven species of mosquitoes belonging to genera Culex, Anopheles & Mansoni are known to be the vectors of JE in India (7).

The maintenance and spread of JE virus appears to be through a pig-mosquito-pig cycle. The pigs act as 'amplifiers' of the virus in the natural cycle of JE. Pigs suffer from a clinically inapparent infection. Man serves as 'dead end' for the infection because of transient and low levels of circulating viruses in his blood (9). Based on experimental and epidemiological studies, it is believed that buffaloes and cattles are probably not involved in the epidemiology of this disease (10). Birds belonging to the family Ardeidae have been incriminated both in the maintenance and dissemination of JE viruses in Japan. Similar observations have been made in India (11). Chickens, ducklings, pigeons and sparrows have all been demonstrated to develop viraemia when experimentally infected. They all can transmit the virus to fresh birds but have not been found as important hosts in India.

It is believed that most infected persons do not develop the disease. During epidemics the attack rate is 0.5/1,00,000 population at risk and the ratio of apparent to inapparent infection is estimated as 1 : 300 to 1 : 1000 (8).

CONTROL OF JAPANESE ENCEPHALITIS

Theoretically three levels of prevention exists (12, 13).

a) **Mosquito Control** — Control of mosquito population with insecticides has several problems as has been the experience in the National Malaria Eradication Programme.

b) **Immunization of pigs** — Live attenuated vaccine has been successfully used in Japan, China and Korea for the vaccination of pigs. This is difficult to achieve especially in rural India where pigs are only reared as a food source by small farmers and mass pig rearing is not an industry. Building of piggeries away from human dwellings and making them mosquito proof can be attempted in India but is difficult to achieve as pigs are reared as scavangers also (9)

c) **Immunization of man** — At present mainly two types of JE vaccines are being used for human immunization.

   1. Formalin inactivated mouse brain vaccine, used mainly in Japan, Korea, Taiwan & Thailand and being produced in India by CRI Kasauli.

   2. Formalin inactivated primary hamster kidney cell culture JE vaccine being used only in China.

Both these vaccines have been found to be effective and safe. Because of the low endemicity and very low attack rates in epidemics, general use of JE vaccine is not recommended in human beings. However if the vaccine is to be used the following are the guidelines :

DOSE — Two doses of the vaccine 1 ml each (0.5 ml for children less than 3 years) administered subcutaneously at an interval of 7-14 days (6) are required for primary immunization. A third dose is given after 6 months to 1 year. Booster dose is required every 3 years, however in non-endemic zone it can be given every 4 years.

STORAGE — The lyophilized vaccine must be kept away from direct sunlight and at a temperature of less than 10°C. Vaccine vial once opened for use should not be retained for further use.

REACTIONS — No serious reactions are known to be associated with this vaccine. Rarely redness, swelling or pain may be seen at the site of injection which disappears within few days. In some cases headache, chills, fever, malaise etc. may be observed.

CONTRAINDICATIONS — High fever, cardiac & liver diseases, diabetes mellitus, malignancies, hypertension and history of convulsions are the contraindications to the use of this vaccine. Although no adverse reactions have been observed in pregnant women, it is advisable to avoid vaccination during pregnancy, unless it becomes essential in the face of an outbreak.

CONCLUSIONS

To prevent the menace of this disease, following methods are suggested :

1. Construction of piggeries away from human dwellings and making them mosquito free.
2. Use of indegenously produced newer drugs for the control of vector.
3. Better surveillance system should be formulated for the endemic states so that an early warning system for JE outbreaks may be developed.
4. Mass vaccination is not the solution to control JE. Moreover, vaccine induced protection appears only after one month of immunization. However vaccine may be given to children in those endemic areas where the disease primarily affects the pediatric age group. It should also be given to the people who live in close proximity of the known amplifier host of the disease i.e. pig.
5. Further research may be carried out to develop better and more cost effective tissue culture vaccine against JE.

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Recommendations

1. More reliable data need to be available to know the exact incidence of morbidity and mortality with this disease. Diagnostic facilities should be made more widely available.
2. The emphasis of prevention at present should be on vector (Mosquito) and reservoir (Pig) control. Mass immunization of people in the endemic area can not be recommended at present.

Cold Chain : Maintenance 10

A.K. Dutta

Most vaccines lose their potency by heat and exposure to sunlight. Vaccines administered with lost potency will not protect the individual and will only give a false sense of security. Potency once lost cannot be restored. To keep vaccines potent, they should be kept at recommended temperatures from the manufacturer to the point of use in the recipient. The system of transporting, storing and distributing vaccine in a potent state at right temperature is known as 'cold chain'. The heat sensitivity of various U I P vaccine in descending order is Polio, Measles, BCG, DPT, Typhoid and TT. Table I gives the recommended temperatures for storage of vaccines :

Table I – Recommended Temperatures for Storage of Vaccines

Vaccine	Temperature	Duration for which vaccine remains potent from the date of manufacture	Remarks
1. Oral Polio Vaccine	< 20°C 2°C to 10°C	1 year 3 months	Avoid repeated thawing. Keep on ice while using.
2. Measles*	0°C to 2°C 4°C to 8°C	2 years 8 months	
3. BCG*	4°C to 8°C	1 year	Use within 3 hours
4. DT (Dual Antigen)	4°C to 10°C	2 years	Must not be freezed
5. DPT (Triple antigen)	4°C to 10°C	1½ years	Must not be freezed.

Vaccine	Temperature	Duration for which vaccine remains potent from the date of manufacture	Remarks
6. Typhoid	4°C to 10°C	1½ years	– do –
7. Tetanus Toxoid	4°C to 8°C	1½ years	– do –

* For reconstitution use only (4°C – 8°C) cold diluent. Keep on ice and use within 3 hours.

:

Temperature in ordinary chamber of fridge : 4°C to 10°C and in the ice chamber : 0°C to 4°C. For lower temperatures use deep freeze.

The details of cold chain maintenance in Government sector can be obtained from the manual prepared by Ministry of Health & Family Welfare (1) or from that prepared by Potdar and Shah for IAP. (2). However some practical aspects are emphasized in the following paragraphs :

CARE OF THE REFRIGERATOR

For proper functioning of the refrigerator following points should be kept in mind :

1. Properly fitting plug and socket should be ensured.
2. Servo/automatic voltage stabilizers be used to avoid voltage fluctuations.
3. Fridge to be kept at least six inches from the wall and in a relatively cool room.
4. Alternate source of electricity can be managed by a portable generator in areas of frequent and long hours of power failure.

VACCINE STORAGE IN REFRIGERATOR

For optimally storing the vaccines in refrigerator following guidenlines should be adhered to :

1. No vaccine should be kept in the door panel.
2. DPT, DT, Typhoid (phenolized) *should never* be kept in the freezer chamber of the refrigerator. These vaccines should be kept in the lower compartments.
3. OPV vial in current use should be kept in central compartment of the refrigerator to avoid repeated freezing and thawing. OPV vials not in use should be stored in the freezer chamber (if space permits) or in the chamber nearest to it.
4. BCG and measles vaccine can also be stored in either the freezer or the shelf nearest to the freezer.
5. Vaccines should be kept in a thermocol box/vaccine carrier containing ice packs during the period in which the fridge is being defrosted.
6. Fridge should be used exclusively for vaccine purposes as far as possible.
7. Minimum stock (Not more than 1 month's requirement) of vaccines should be kept in the fridge at a time.
8. Single dose vials may be preferred.
9. During a vaccination session, which may last for long duration, vials of vaccines taken out of refrigerator should be kept in a cup/card board box containing ice cubes.

TRANSPORTATION OF VACCINES :

Transporation of vaccines requires the same precautions irrespective of its destination (from district to PHC, from PHC to subcentre or from chemist to private clinic etc.etc).

Two main principles to be kept in mind while transporting the vaccine are :

a) The temperature in the container should be below 8°C and enough ice should be available to ensure this.

b) DPT/TT/Typhoid vaccines should not be frozen—So they should not be kept in direct contact with the ice cubes.

Various equipmetns are available for this purpose. selection will depend upon the quantum to be transported and availability of the equipment.

Thermocol Box/Thermos Flask — They should be wide mouthed. adequate amounts of ice, kept in one or more polythene bags, should be used in them for transportation. This is done to avoid direct freezing contact of DPT/TT/Typhoid vaccine with ice and also to prevent the possible seepage of water resulting in damage to the vaccine labels etc.

Cold Box/Vaccine Carriers — These are insulated boxes with required number of solidly frozen ice packs. They have separate chambers for various vaccines. These are very suitable for the transport of large amounts of vaccine (e.g. from district centre to PHC).

It is always prudent to fix up vaccination days at peripheral centres and to transport the required amounts of vaccine to that place on the same day. All left over vaccines at the end of the day should be discarded as far as possible and not returned to the main stores.

Thus if above mentioned precautions are taken during storage and transportation of vaccines, there is no reason why cold chain cannot be maintained properly.

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Cold Chain : Pit Falls and Remedies

11

Raju C. Shah

With the inclusion of heat labile vaccines like Oral Polio Vaccine (OPV) and measles vaccine in the Universal Immunisation Programme (U.I.P.) maintenance of cold chain has assumed paramount importance. Our country is very vast with different types of geographical terrains requiring different strategies for maintenance of cold chain.

Vaccines are handled by different categories of people at various levels especially in the field. Their knowledge and attitude about cold chain maintenance is very important for success of the programme. These people include E.P.I. officers, P.H.C. doctors, Non-medical supervisors, Health assistants, Multipurpose workers, Auxillary midwife nurses and many others.

Power supply plays very important role because the majority of storage equipments run on electricity. Continuous supply is not always guaranted.

Cases of paralytic poliomyelitis in vaccinated children are being reported more frequently in Indian literature (1, 2). In majority of instances probable cause of vaccine failure is failure of cold chain maintenance. Potency testing at various places show that only 45 to 48% of tested sampels are potent (3, 4).

Poor knowledge and carelessness of health workers, poor maintenance of vaccine carriers and refrigerators, frequent power cuts, poor transportation, long distances and poor supervision and monitoring are the major underlying causes of cold chain failure. In South African epidemic in 1982 loss of potency during transportation and storage in field was well proven (5).

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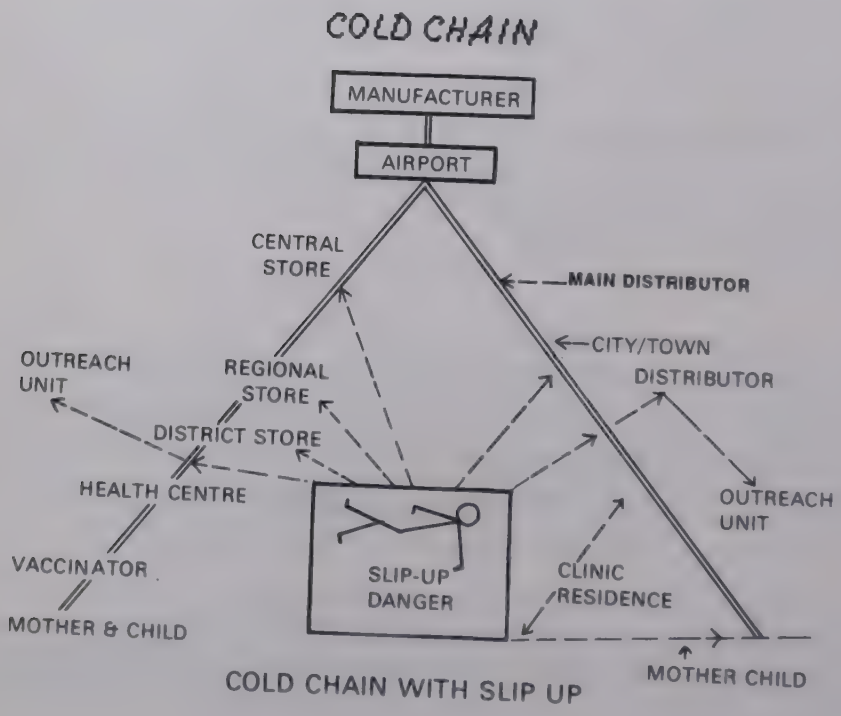
PITFALLS

Fig. 1 shows the various vulnerable zones of cold chain failure.



COLD CHAIN WITH SLIP UP

I. GOVERNMENT SECTOR

A. Problems of Equipments

1. **At Airport** — Walk-in coolers are not supplied at all airports. There is no proper liaison between suppliers and regional store people. No responsible person remains at the airports to take care of vaccines when they arrive.

2. **Transportation** — Various factors like (a) long distances, (b) poor roads & transport system and (c) Non-availability of air-conditioned vehicles or adequate vaccine carriers, are responsible for disruption of cold chain during transportation.

3. Field Level

a) **Electricity failure** — Unfortunately it is almost a routine feature in almost all parts of India including metropolitan cities. In Gujrat, daily electricity load shedding takes place on an average for 2 hours, while in U.P. it may be for as long as 8-10 hours a day.

b) **Mechanical faults of cold chain equipments**— Many persons handle the refrigerators but no one is really responsible for its maintenance. Even for minor faults, repairs and replacement of parts take very long time.

c) **Use of refrigerator for other purposes** — It is common to see drinking water, cold drinks or even eatables being stored in the same refrigerator.

d) **Poor maintenance of vaccine carriers** — Often the vaccine carriers are without straps or have their inner lining torn. In many of them even the lid does not close itself. What is worse is that in some places, even when the vaccine carriers are alright, they are either not being used or being used improperly.

e) **Ice pack** — Usually inadequately available or inadequately used.

B. Problems of Personnel

The problems related to personnel are even more than those related to equipments. In fact many of the problems seen in equipment are person related only. Results of a recent KAP (Knowledge, attitude & practices) study of 50 postgraduates of pediatrics, 50 nurses and 30 interns are rather startling in this regard.

Only 8% of postgraduates knew correct temperature ranges for maintenance of cold chain at different levels. 50% of postgraduates had no idea of field level cold chain maintenance. Nurses were only aware that the vaccines should be kept in refrigerator but did not know the details of the same. Among interns only 6% had the knowledge about vaccination schedule of E.P.I. None of them had knowledge about cold chain or maintenance of temperature for different vaccines.

Apart from poor knowledge, the problem of personnel are common at all levels and they can be summarised as follows :

a) Inadequate numbers.

b) Untrained or poorly trained.

c) No incentives or disincentives & inadequate supervision.

d) Repeated transfers.

e) Engaged in other pressing work like family planning, epidemic outbreak etc.

f) Lack of inter personal coordination.

g) Careless or indifferent attitudes.

II. NON-GOVERNMENT SECTOR

Situation in the private sector is probably even worse than in the government sector.

A survey of 20 medical stores selling vaccines and 30 general practitioners revealed that in private sector usually there is no monitoring or supervision at any level. Mostly untrained personnel are handling vaccines specially in the medical stores. They have no knowledge about temperature requirements of various vaccines. Most of them in any case sell only DPT/DT or TT. These are often kept in freezers or sometimes even on the shelfs at room temperature. None of the practitioners were aware of routine precautions required for storage or tansportation of vaccines or availability of potency testing facilities.

REMEDIAL MEASURES

In view of observed pitfalls, following remedial measures are suggested :

1. Supply of equipments in adequate amounts to all the field centres should be ensured. This includes : working refrigerators, vaccine carriers and ice packs.

2. Instructions regarding maintenance and use of various equipments should be made available at all the centres.

3. Refrigerator mechanic should be available at all the centres. Replacement of parts etc. should be quick. Some funds should be available with medical officers for getting parts from market.

4. Mini generators should be provided at all the centres.

5. Proper training and retraining of all categories of personnel is absolutely essential. Since immunisation is a complex process involving many disciplines, the training in immunisation has to be multidisciplinary (7).

   In this context training of undergraduates & interns is vital as they are our future medical officers.

6. Compulsory certificate course of 3-5 days should be there for all practitioners who wish to administer vaccines. Regulations for medical stores selling the vaccines should be prescribed and strictly enforced.

7. Supervision and monitoring of cold chain at all levels should be provided. Facilities for potency testing should be made available more widely and it should be made compulsory for all centres/practitioners etc. to get routine potency testing done, results of which should be widely communicated.

8. Liaision between Central Ministry, State Government, E.P.I. officers, I.A.P., Medical Officers of P.H.C. and private practitioners is required. Passing information as fast as possible and repeated open forum discussions and dialogues at all levels will help solving problems and improving the situation.

CONCLUSIONS

Maintenance of cold chain is difficult but not impossible. Strong determination, proper training, positive attitudes of people of all the cadres, proper maintenance of equipments, close supervision and adequate monitoring can go a long way in fulfilling our dream of universal immunization by potent vaccines.

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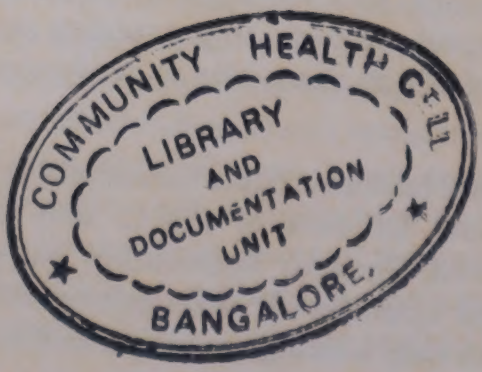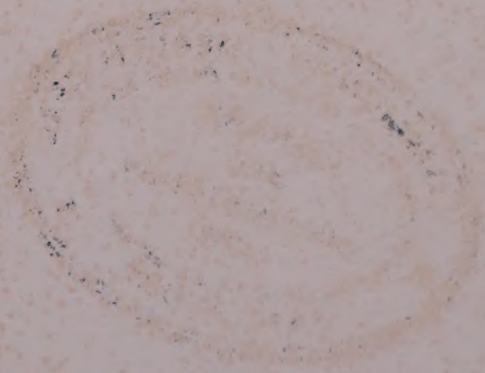
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